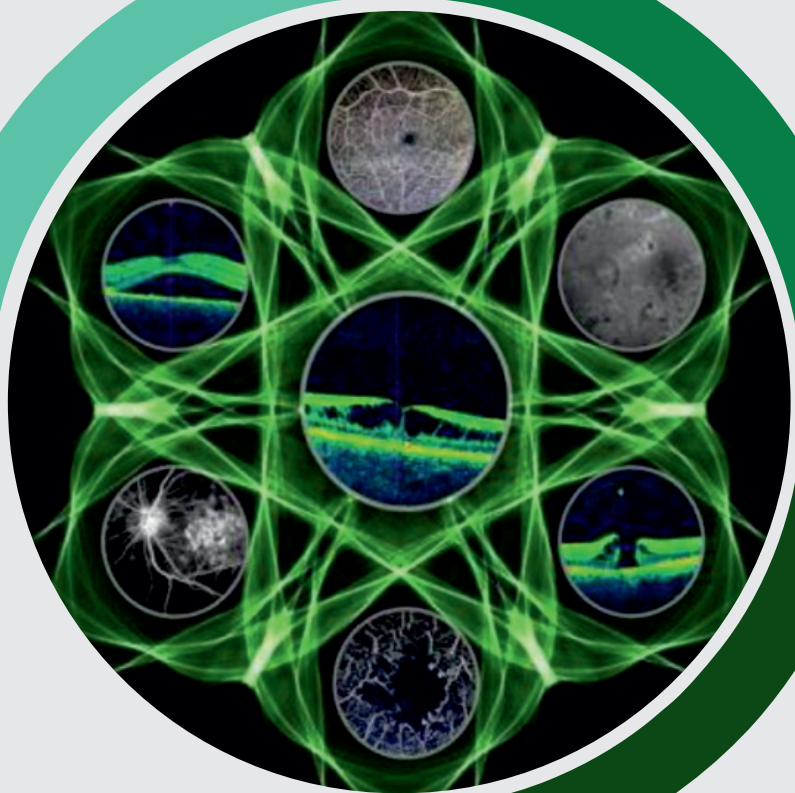




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OPHTHALMOLOGY CASES & HYPOTHESES

SPECIAL ISSUE

A new theory of the emergence of eye diseases based on the imbalance of human microbiota. A critical review of the literature

GUEST EDITORS

Suleyman Kaynak

Nikolay P. Pivovarov

Vitovska Oksana



SPECIAL ISSUE

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SPECIAL ISSUE

GUEST EDITORS

Professor Vitovska Oksana

*Bogomolets National Medical University,
Kyiv, Ukraine*

Suleyman Kaynak, MD, PhD

*Retina Ophthalmic Research Center,
Department of Ophthalmology, Izmir, Turkiye*

Nikolay P. Pivovarov, MD, PhD

*Professor, Ophtahlmologist,
Pescara Corso Vittorio Emmanuele
406 Studio Oculistico Renato Minicucci, Italy*

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SPECIAL ISSUE

PREFACE

This article presents an innovative perspective on the emergence of human diseases, particularly eye diseases, through the lens of Chaos Theory. The authors propose that all cells in the body are arranged in fractal patterns, and diseases arise when these fractal structures are disrupted. The foundation of this disruption is an imbalance among epithelial cells, the microbiota, and surrounding immunoglobulins, collectively termed the “triumvirate,” drawing an analogy with ancient Roman history.

The triumvirate concept is groundbreaking, as it posits that this symbiotic relationship regulates all organs and tissues, functioning as a “clinical attractor.” This self-sustaining system of interactions between the microbiota, mucosal membranes, and antibodies is hypothesized to maintain the balance and health of various body tissues. The identification of five clinical attractors – the gut, urogenital, respiratory, ocular, and aural attractors – further refines our understanding of disease mechanisms.

Particularly compelling is the hypothesis that peptides on the surface of MHC-1 of somatic cells are epitopes of the microbiota. This suggests that each cell type, depending on its evolutionary history, harbors specific microbiota-related antigens. The example of peptides associated with MHC-1 cells of the optic nerve and visual tract underscores the potential for targeted therapeutic interventions. The notion that restoring the balance between the ocular microbiota and surrounding antibodies can halt the progression of optic nerve atrophy and improve visual function is particularly promising.

Overall, this theory offers a paradigm shift in understanding the origin and treatment of human diseases, providing a novel framework that integrates microbiota-immune interactions and fractal biology. This article is a valuable contribution to the field, presenting a comprehensive and innovative approach that warrants further exploration and validation.

Likewise, I would like to express my appreciation for the tremendous efforts made by the author, Rasim V. Hajiyevev MD, PhD, Professor, who submitted the paper to this special issue. I also sincerely thank the Guest Editors of this Special Issue and the editorial team of the Journal Ophthalmology Cases & Hypotheses (OCH).

Professor Vitovska Oksana

*Bogomolets National Medical University,
Kyiv, Ukraine*

SPECIAL ISSUE

This article offers an insightful and progressive hypothesis linking microbiota imbalance to the development of both ocular and systemic diseases. Through a robust review of existing literature combined with the authors' own research, the paper advocates for a shift from traditional reductionist views in medicine to a model that embraces the complexities of chaotic systems. This approach illuminates the intricate relationships between microbiota, human epithelial cells, and immunoglobulins.

The paper introduces a pioneering perspective on disease genesis, emphasizing the chaotic and fractal nature of cellular organization. It suggests that the arrangement of cells in fractal patterns is fundamental to health, and that diseases may stem from disruptions in these patterns. Central to this disruption is an imbalance in the "triumvirate" of mucosal cells, microbiota, and immunoglobulins—a term evocatively borrowed from Roman history to describe their interdependent relationship.

The hypothesis posits that the fractal structure of cellular arrangement, when disrupted, leads to disease. This disruption is intricately linked to an imbalance among the epithelial cells that interface with the external environment, the microbiota, and the immune system's antibodies. By framing this relationship as a clinical attractor, the article offers a novel framework for understanding how changes in microflora can influence disease states across the body, not just in the eyes but systemically.

This review does more than just challenge existing paradigms; it proposes a comprehensive model that could revolutionize our understanding of health and disease. The integration of chaos theory into systemic medicine provides a valuable lens through which we can re-examine the complexities of human health. This article is a significant contribution to the field, offering new avenues for research and potential therapeutic strategies that could be particularly transformative in the realm of ophthalmology.

Suleyman Kaynak, MD, PhD

*Retina Ophthalmic Research Center, Department of Ophthalmology,
Izmir, Turkiye*

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A NEW THEORY OF THE EMERGENCE OF EYE DISEASES BASED ON THE IMBALANCE OF HUMAN MICROBIOTA. A CRITICAL REVIEW OF THE LITERATURE

Rasim V. Hajiyev MD, PhD, Professor

HAT Medicine Clinic, Baku, Azerbaijan

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ABSTRACT

Purpose

Based on a critical review of the literature, as well as our own research and observations on the causes of eye diseases (dry eye syndrome, glaucoma, retinal diseases, optic neuropathy), we propose a new hypothesis about the role of microbiota imbalance in the development of both ocular and systemic diseases. This review attempts to move away from the existing reductionist approach. It attempts to explain that the laws of Chaos underpin systemic medicine.

Conclusions and importance

From the new perspective of Chaos, the emergence of all human diseases, particularly eye diseases, is considered. All cells in the body are arranged in the form of fractals. In diseases, the fractal structure of cell arrangement is disrupted.

The basis for the emergence of diseases and the disruption of the fractal structure of cells lies in the imbalance between the epithelial cells of humans that come into contact with the external environment, the microbiota, and the surrounding immunoglobulins. This symbiosis between mucosal cells, microbiota, and immunoglobulins is called the "triumvirate," by analogy with ancient Roman history.

This triumvirate regulates all organs and tissues of the body. This entire system represents a "clinical attractor." The term "clinical attractor" reflects the idea of a self-sustaining system where interactions between the microbiota, mucosal membranes, and surrounding antibodies regulate various tissues in the body.

There are five clinical attractors in the body: gut attractor, urogenital attractor, respiratory attractor, ocular attractor, and aural attractor.

It is hypothesized that peptides on the surface of MHC-1 of somatic cells are epitopes of the microbiota. Each cell of an organ or tissue in the human body has MHC-1 on its surface, which is an epitope of a specific microbiota. The specific antigenic determinant of the microbiota on the cells of the conjunctiva, choroid, and retina depends on the evolutionary history of that specific tissue.

For example, a peptide associated with MHC-1 cells of the optic nerve and visual tract is characteristic of the ocular microbiota. Restoring the balance between the ocular microbiota and the surrounding antibodies can stop the progression and improve the visual functions of patients with optic nerve atrophy.

This theory provides a new perspective on the origin and treatment of all human diseases.

Keywords: Microbiota, optic neuropathy, affinity, peptide exchange, adaptive immunity, major histocompatibility complex, epitope, systems biology, chaos, fractals, dry eye disease

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Address for correspondence:
Rasim V. Hajiyev MD, PhD, Professor
HAT Medicine Clinic, Baku, Azerbaijan
Email: rasim.gadjiev@gmail.com

Introduction

Since Descartes and the Renaissance, science, including medicine, has taken a distinct path in its analytical evaluation of the natural world.^{1,2} This approach can be described as one of “divide and conquer,” it is rooted in the assumption that complex problems are solvable by dividing them into smaller, simpler, and thus more tractable units. Because the processes are “reduced” into more basic units, this approach has been termed “reductionism” and has been the predominant paradigm of science over the past two centuries. Reductionism pervades the medical sciences and affects how we diagnose, treat, and prevent diseases.

The surgery operates on a reductionist level. The triumph of reductionism was the discovery of the DNA molecule by Watson and Crick.³

While it has been responsible for tremendous successes in modern medicine, there are limits to reductionism, and an alternative explanation must be sought to complement it.

While the implementation of clinical medicine is systems-oriented, the science of clinical medicine is fundamentally reductionist. This is shown in four prominent practices in medicine: (1) the focus on a singular, dominant factor, (2) emphasis on homeostasis, (3) inexact risk modification, and (4) additive treatments.⁴

Focus on a singular factor

When the human body is viewed as a collection of components, the natural inclination of medicine is to isolate the single factor that is most responsible for the observed behavior. Much like a mechanic who repairs a broken car by locating the defective part, physicians typically treat disease by identifying that isolatable abnormality. Implicit within this practice is the deeply rooted belief that each disease has a potential singular target for medical treatment. For infection, the target is the pathogen; for cancer, it is the tumor; and for gastrointestinal bleeding, it is the bleeding vessel or ulcer.

The alternative explanation that has received much recent attention, due to systems biology, is the systems perspective

While the success of this approach is undeniable, it leaves little room for contextual information

Emphasis on homeostasis

The homeostasis principle was discovered by Walter Bradford Cannon in 1929.⁵ The homeostasis principle is the property of a physiological system to regulate its internal environment to a given set point in the presence of a specific stimulus producing changes in that variable”⁶

The control activity in the body is guaranteed by the arrangement of the control center (composed by nervous and endocrine systems), sensors, and effectors. For decades, homeostasis has been a vital, guiding principle for medicine

Since then, homeostasis has been incorporated into clinical practice. Illness is defined as a failed homeostatic mechanism, and treatment requires physicians to substitute for this failed mechanism by correcting deviations and placing parameters within normal range.

Consequently, emphasis is placed on static stability/normal ranges and not on dynamic stable states, such as oscillatory or chaotic (seemingly random but deterministic) behavior. Circadian rhythms^{7,8} are an example of chaotic behavior. Failure to include these dynamic states in the homeostasis model may lead to treatments that are either ineffective or even detrimental.⁹

Inexact risk modification

Since disease cannot always be predicted with certainty, health professionals must identify and modify risk factors. The common, unidimensional, “one-riskfactor to one-disease” approach used in medical epidemiology, however, has certain limitations.

Doctors are trying to identify risk factors for diseases, such as hypertension, through scientific research.¹⁰ But it is impossible to take into account all risk factors for hypertension.¹¹

Additive treatments

In reductionism, multiple problems in a system are typically tackled piecemeal. Each problem is partitioned and addressed individually. In coronary artery disease, for example, each known risk factor is addressed individually, whether it be hyperlipidemia or hypertension.

Cardiologists treat coronary artery disease with one method, while gastroenterologists treat intestinal ulcers with a different method. And in principle, these diseases may be based on the same cause.

Limitations to Current Medical Science

The science underlying our medical practices, from diagnosis to treatment to prevention, is based on the assumption that information about individual parts is sufficient to explain the whole. But there are circumstances in which the complex interplay between parts yields a behavior that cannot be predicted by the investigation of the parts alone. The failure to account for these circumstances is the common denominator for the explanations of why the aforementioned practices are, in many cases, inadequate.

So how should these complexities be addressed? Is there a formal method that can explain how the pieces create the whole? How do we shift our lens from the parts to the system?

Systems biology

The answers to these questions may come from a relatively new branch of science called systems biology or systems medicine^{12,13,14,15,16}

But this system also does not work. It doesn't work because the laws of Chaos are not taken into account. Although it must be admitted that there are studies devoted to the theory of chaos in medicine.^{17,18,19}

But these studies do not answer the question of how the human body works and why diseases occur. The fact is that the theory of Chaos does not fit well into the modern idea of medicine in general.

Chaos theory from new positions

We believe that systemic medicine is based on the laws of Chaos. Chaos theory was called by Feynman himself one of the three triumphs of the 20th century, along with the theory of relativity and quantum mechanics. In 2013, the journal Nature stated that this is one of the most important misunderstood theories of the 20th century.²⁰

Lorenz an American mathematician and meteorologist was the pioneer of the chaos theory. He studied weather patterns he began to realize that they did not always change as predicted. Minute variations in the initial values of variables in his twelve-variable computer weather model would result in grossly divergent weather patterns. This sensitive dependence on initial conditions came to be known as the butterfly effect²¹

Chaos theory explains that within the visible randomness of complex, chaotic systems, there are inherent repetition, patterns, self-organization, interconnectedness, self-similarity, and constant feedback loops.

Fractals

Today, fractals form part of the visual identity of chaos. As infinitely complex objects that are self-similar across all scales, they represent dynamical systems in all their glory

The birth of fractal geometry is usually associated with the publication of Mandelbrot's book in 1977.²² Fractal geometry describes structures that repeat at different scales with similar or identical shapes. In organic matter, cellular structures and enzymes²³ often exhibit fractal characteristics due

to their hierarchical organization and repetitive structural elements across different levels. This is because fractal geometry reflects universal principles of organization and formation in complex systems, whether organic or inorganic.

Quantitative analysis of the branching of the respiratory tract showed that it has a fractal structure.²⁴

The fractal structure is also characteristic of liver tissue.^{25,26} Cells of the gastrointestinal system also have a fractal structure.²⁷

Thus, we see that all cells of the human body are in the form of fractals. Violation of the fractal structure leads to the occurrence of diseases. We can see this in the example of eye angiography (Figure. 1,2,3).

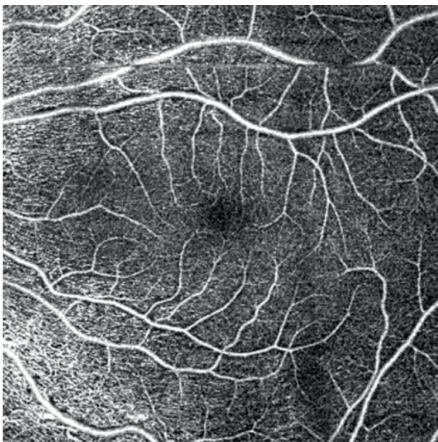


Figure 1. Normal fractal structure of the eye's capillaries.

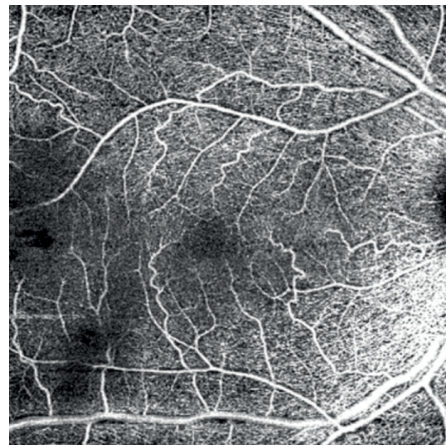
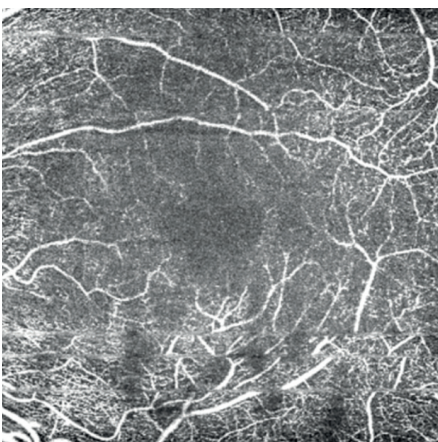


Figure 2, 3. In retinal diseases, the normal structure of the capillaries changes. Chaos ensues

We have hypothesized that the fractal structure of the body's cells is maintained by the state of equilibrium between the body's microbiota and the surrounding immune cells – immunoglobulins. Let's examine the theory of Chaos in more detail.

Laws of dialectical materialism in the theory of Chaos

The laws described in Chaos coincide with the laws of dialectical materialism. The second law of dialectical materialism states that everything in the world obeys the principle of unity and the struggle of opposites.²⁸

An atom maintains its structure due to the 'struggle' between the positively charged nucleus and the negatively charged electrons orbiting around it. Each elementary particle corresponds to an antiparticle; both have almost identical characteristics, except that they have opposite electric charges. If the particle is neutral, then the antiparticle is also neutral, but they may differ in other characteristics.

It is in the struggle of opposites (The Unity of Opposites) that particles are born and their opposites immediately arise.

We can observe manifestations of these laws in the example of the retina. The retina consists of an outer layer (red color Figure. 4), which includes the pigment epithelium layer and the photoreceptor layer, and an inner layer (green

color, bipolar ganglion cells, Müller cells). These two layers are in opponent relationships with each other (Figure. 4).³⁰

In diabetic retinopathy, only the inner part of the retina is affected, and photoreceptors remain intact.

For the treatment of diabetic retinopathy, we use pan retinal laser coagulation. By destroying the outer layer of photoreceptors, we improve the condition of the inner layer. That is why pan-retinal coagulation is the main method for treating diabetic retinopathy.²⁹

With a high degree of myopia or with “parquet type” (tessellated fundus), diabetic retinopathy does not develop.³⁰

In cases of high myopia or tessellated fundus, diabetic retinopathy does not develop. These two layers of the retina are in opposition to each other. This phenomenon manifests itself throughout the body.

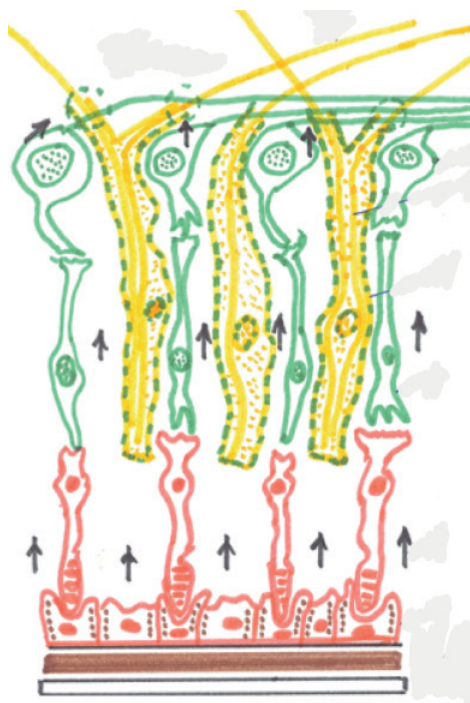


Figure 4. The outer part of the retina is colored red, the inner part of the retina is colored green. Yellow represents Müller cells, which contain the yellow pigment lipofuscin. Atrophy of Müller cells in the outer plexiform layer results in hard exudates.³⁰

It has been shown that optic fibers from the periphery of the retina go to the superior colliculus, while fibers from the center of the retina go to the lateral geniculate body. Azerbaijani neurophysiologists have established that these two channels are in an opposing relationship. When one channel is stimulated, the activity of the other channel is suppressed and vice versa.³¹ It is interesting to note that when gastrointestinal diseases occur, brain diseases or dementia³², are less likely to occur, and vice versa. When there is a gynecological pathology, there may not be any eye diseases. Sometimes gynecological diseases disappear, and optic neuritis,²⁴ or retinal diseases³⁴ may suddenly appear. So throughout the body.

Cells cannot exist without competition with other cells for habitat and food resources. Competitive interactions between cells are the basis of many homeostatic processes in biology.³⁵

This competition also manifests itself in the macroorganism. In recent years, many articles have appeared devoted to the role of microbiota in the occurrence of various human diseases. The human body cannot exist without microbiota (the struggle of opposites).

In particular, the role of gut microbiota in the occurrence of dry eye syndrome^{36,37} and glaucoma has been established.^{38,39,40} An imbalance of the microbiota and the human immune cells surrounding them can lead to various eye diseases: diabetic retinopathy, uveitis, and orbitopathy.⁴¹

Studies conducted by some authors on clinical cases in patients suggest the possible role of gut microbiota in the development of retinal diseases. The question arises, how does gut microbiota cause retinal diseases?

Evolution of the human eye

To answer this question, we must turn to the evolution of man and the eye.

Considering the aforementioned literature data on the role of microbiota in the occurrence

of eye diseases, we believe that the human organism exists thanks to microbiota. Microbes colonize and reside on the mucous membranes of cells that are in contact with the external environment. The aggression of microbes is restrained by immune cells, creating a state of dynamic equilibrium (the struggle of opposites). After unicellular organisms, coelenterates appeared. That is, an environment (intestinal tube) populated by microorganisms – microbiota – emerged, which began to regulate all the life activities of the macroorganism.

The immune system of Hydra developed due to the need to control the resident microbiota. Protection against invasive pathogens is secondary compared to the need to regulate commensals.⁴³

The microbiota of the coelenterate gut tube was surrounded by primary immune cells. A state of balance emerged. At that time there was no acquired immunity and the state of equilibrium was maintained by innate immunity.

Authors also review observations that indicate that resident beneficial microbes affect the animal's behavior by directly interfering with neuronal receptors.⁴⁴

Also, the formation of the future eye system begins with Hydra. Sensitive opsins were also found in hydra nerve cells. The analysis of the hydra opsin gene suggests that hydra and human opsins have a common origin.⁴⁶

Box jellyfish, which are also coelenterates, also have eyes.^{46,47,48} These are primitive eyes that developed due to the functioning of the gut microbiota. This is why a number of eye diseases are associated with disturbances in gut microbiota.^{49,50}

The eyes of cuboid jellyfish are primitive, capable of distinguishing light from darkness. Then, in the process of evolution, the eyes improved and other newly formed microbiota began to take part in their development (for example, the microbiota of the genitourinary tract and others).

In addition, the conjunctiva of the eye itself is also populated by microbiota and regulates the

conjunctiva, cornea, and iris. However, since at the beginning of evolution the conjunctiva was regulated by the gut microbiota, its disruption can lead to dry eye syndrome, glaucoma, and AMD.

The first clinical attractor

How does the microbiota of the gastrointestinal tract work? The intestine first appeared in coelenterates. A typical representative of coelenterates is a hydra. There has been a huge revolution in biology. The body of a living creature has its own microbes. These microbes surround immune cells.

An entirely new dynamic community has emerged, consisting of the intestinal microbiota, surrounding immune cells, and the epithelial cells of the Hydra "gut." By analogy with ancient Roman history, we gave this community the name *triumvirate*.

This microbiota not only helps digest food,⁵¹ but also regulates all the vital functions of coelenterates. What is an attractor?

An Attractor is a term used to describe any system that remains stable without any changes over time. The simplest attractor is a pendulum-shaped attractor. The attractor is a single point; all trajectories spiral in toward it, like a pendulum slowing down and coming to rest, pulled to the single center of gravity. Complex periodic attractor; indicating a system that repeats itself periodically.

All Hydra cells together with the triumvirate (epithelial cells, microbiota, immune cells) represent the first gastrointestinal, complex clinical attractor.

A change in one of the components of the "triumvirate" can lead to a change in the functional state of the hydra (by analogy with a person, the appearance of characteristic symptoms or diseases). But then, thanks to the lability of the "triumvirate," the work of the immune system returns the clinical attractor to its original state.

Thus, it is the gut attractor triumvirate that determines the entire life activity of coelenterates,

their health, eye condition, timing of division, reproduction and further evolution.

An interesting question is how an imbalance of the gut attractor microbiota and the antibodies surrounding them can lead to dry eye syndrome, glaucoma or AMD?

Interaction of microbiota with immunoglobulins

Our question addresses the complex dynamics between different populations of microbes and the immune system. The competition for resources among microbes and the interaction with antibodies is a multi-layered process.

The microbiota living on mucous membranes is heterogeneous. Various bacteria can be observed there. Even bacteria of the same type differ in their antigenic composition. These microbes compete for resources, for territory. Immunoglobulins appear to be produced by the average determinant of the microbial population.

When different strains of microbes compete for resources, it can alter their numbers and population structure. If more aggressive or extreme forms start to dominate, this can indeed cause a change in the profile of immunoglobulins produced. The immune system, particularly B-cells, is capable of adapting to new antigens by producing immunoglobulins specific to the new dominant strains.

This adaptation may involve:

1. Clonal selection and proliferation of B-cells that are specific to new antigens.
2. The process of affinity maturation, where antibodies become more specific to the antigens they encounter.

The degree of microbial adherence to antibodies, or avidity, is of paramount importance. If microbes were left unchecked, they could completely destroy all the cells in the body, similar to what happens post-mortem. Immunoglobulins restrain microbial aggressiveness. However, if the antigenic composition of microbes changes, their adherence decreases, making them more

aggressive. This impacts the cells, causing changes in their orientation relative to each other, potentially altering the fractal structure of the cells. These alterations can lead to diseases. The speed at which the immune system can restore the original avidity will determine whether the symptoms will disappear. In other cases, changes in the fractal structure can propagate like a “domino” effect, affecting other areas controlled by this attractor.

Thus, the triumvirate system (cells, microbiota, immunoglobulins) is constantly subject to changes (due to constant changes in avidity between microbiota and immunoglobulins) and this is reflected in the functioning of the corresponding clinical attractor.

Thus, the immune system and microbiota are in constant dynamics.

Changes in one system inevitably led to changes in another. If extreme forms of microbes begin to dominate and the immune system does not keep up with the adaptation to new antigens, this can cause an imbalance that can lead to disease.

Competition among microbes can also influence the immune response, leading to changes in inflammation levels and cytokine production. Thus, the immune system and microbiota are in constant dynamic interaction, where changes in one system lead to responses in the other.

The description of microbiota as a system that is constantly changing and recovering indeed resembles the behavior of complex attractors in chaotic systems.”

Chaotic systems are characterized by high sensitivity to initial conditions and unpredictable but deterministic behavior. In biological systems, such as the microbiota and the immune system, similar properties can be observed.

The microbiota can change under the influence of various factors, including diet, environment, and infections, which in turn affects the immune response of the body.^{52,53,54}

These dynamic and unpredictable changes can be considered chaotic because they lead to

nonlinear responses and difficulty in predicting the system's future behavior. Our comparison with a pendulum returning to its original state is also appropriate, since it reflects the idea of a stable state around which a system can oscillate.

Thus, the microbiota and immune system can be viewed as a chaotic system where constant change and adaptation are key characteristics. This highlights the importance of understanding the dynamics of such systems for the development of new treatments and health maintenance.

Our description of the triumvirate of the microbiota, antibodies, and epithelial cells highlights the importance of the interactions between these components in maintaining homeostasis. If we consider them as a single unit, it becomes clear that any disturbance in one of these elements can lead to an imbalance, which then causes pathological conditions. When the immune system fails to quickly adapt to changes in the microbiota or antigenic composition, it can indeed lead to chronic inflammation.

Self-organised criticality (SOC)

The last decade and a half has seen an ardent development of self-organized criticality (SOC), a new approach to complex systems.⁵⁵

"If we keep pouring grains of sand, a heap will soon form. The heap will become steeper and steeper until the pile of sand reaches a critical state. It is unknown when the next grain might cause an avalanche. A catastrophe will occur, but the system will not leave the critical state. The heap of sand will remain just as steep. It will take very few new grains for another avalanche to occur. Avalanches will continue to occur again and again. Their size can vary, for example, from small landslides to large ones involving 30-40% of the sand. And yet, it will remain in a critical state.

This is a very interesting phenomenon of self-organized criticality. This phenomenon is found everywhere. It is found in evolutionary theory, population dynamics, social phenomena, and medicine.

Neurons in the brain are constantly in a state of self-sustaining criticality. Any frequent disturbances can trigger cascading activations of neurons.⁵⁶

"Self-organized criticality in immunology

How can the theory of self-organized criticality be applied to humans? It manifests in everything, especially in immunity.

With the exception of passive immunity, humans have two main types of immunity—innate and acquired immunity. The former evolved in primitive organisms, and the latter appeared in vertebrates. Innate immunity reacts quickly (between several hours to days), while the latter reacts slowly (days to years).⁵⁷

The cellular components of innate immunity consist of macrophages, natural killer (NK) cells, and mast cells, while the cellular components of acquired immunity are made up of T and B cells.⁵⁸

IgM is often associated with the initial stage of infection, as it is produced first in response to an antigen.⁵⁹ An increase in IgM levels may indicate a recent infection. IgG, on the other hand, indicates a more mature immune response and can suggest an ongoing or past infection.⁶⁰

Studying other types of antibodies can also aid in diagnosis. For example, IgE is elevated in allergic reactions and some parasitic infections.⁶¹ IgA is important for the protection of mucous membranes and can be linked to immune disorders in these areas.

Humans suffer from a vast number of diseases of the digestive organs, respiratory organs, urogenital organs, and the eyes. All these diseases are related to changes in the balance of immunoglobulins in the blood. However, we cannot determine how changes in the balance of immunoglobulins in the blood influence the development of hundreds of diseases. Why?

Mammals make five classes of antibodies, each of which mediates a characteristic biological response following antigen binding.⁶²

Immunoglobulins circulating in the blood are produced against various microbiota present in the human body (gut microbiota, urogenital microbiota, respiratory tract microbiota, ocular and aural microbiota Figure. 5). It is interesting to note that there are 5 types of microbiotas and 5 types of immunoglobulins in the body. Is this a coincidence or not?

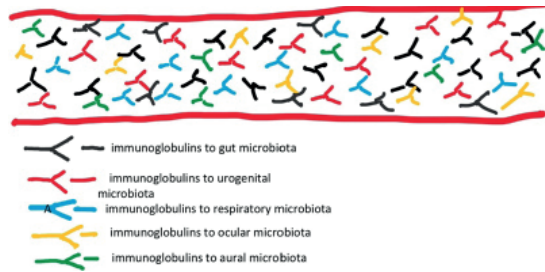


Figure 5. Schematic representation of immunoglobulins responsible for different microbiota in the blood.

Triumvirate

We have called the symbiosis of the microbiota, the surrounding secretory immunoglobulins, and the epithelial cells of the mucous membranes that contact the external environment (for example, the epithelium of the digestive tract) a 'triumvirate,' by analogy with ancient Roman history. Each epithelial cell contains a major histocompatibility complex (MHC-1) on its surface.

On the surface of MHC class-I complexes, there are peptides that are fragments of intracellular proteins. These peptides can be either self-derived (originating from normal cellular proteins) or non-self (such as viral proteins during infections).

Cytotoxic T-lymphocytes (T-killers) recognize these peptides through their T-cell receptors (TCR). If the TCR detects a peptide that is different from normal self-peptides (such as a viral or mutant protein), the T-cell becomes activated and can destroy the infected or abnormal cell.⁶³

What are peptides that are fragments of intracellular proteins? It can be assumed that these are active fragments of antigens of the

body's own microbiota (epitopes of microbiota antigens). SIgA located in the mucous membranes of the microbiota on one side can be bound at one end to the microbiota epitope MHC-1 of the epithelial cell, and at the other end can be bound to microbes in the mucous membranes. That is why they are characterized by dimerism (Figure. 6).

Since these are fragments of the body's own microbiota, for which immunoglobulins have already been produced, T-killers do not react to them. The immune system of the body monitors this, which in some cases can test epitopes and, when changing the antigen composition of the microbiota or changing its affinity with antibodies, trigger a new immune response.

There is a constant change in the antigens of the microbiota in the body, and accordingly, the hypervariable regions (CDR-complementarity-determining regions) of immunoglobulins that interact with this microbiota are also changing. Even hypervariable regions of immunoglobulins, such as CDR, exhibit fractal geometry.⁶⁴

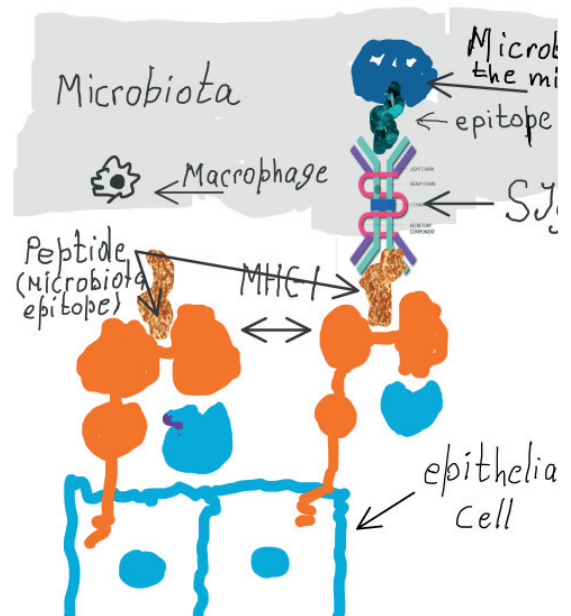


Figure 6. Schematic representation of the 'triumvirate'. Peptides on the surface of MHC-1 are epitopes of the microbiota. Secretory immunoglobulins monitor this, which in some cases can test the epitopes and change their structure when the antigen composition of the microbiota changes

Then the peptide protein of somatic cells immediately changes. This process occurs constantly. Moreover, this is characteristic of each clinical attractor with its own microbiota.

The balance of ocular microbiota helps protect the eye from pathogens, modulates the immune response, and maintains the integrity of the tear film. Disruption of this balance can lead to various ophthalmological conditions, such as conjunctivitis, keratitis, and dry eye syndrome

What ensures the normal balance in the triumvirate?

1. The total amount of immunoglobulins in the blood is relatively constant. They are all distributed among the five clinical attractors. Each microbiota is characterized by a certain amount of immunoglobulins. An increase in the amount of immunoglobulins for gut microbiota can lead to a decrease in the amount of immunoglobulins for urogenital microbiota.
2. Each microbiota is characterized by a specific type of immunoglobulins. For example, gut microbiota is more characteristic of immunoglobulin type IgA. Although other immunoglobulins can also act there.
3. Affinity. The degree of binding of immunoglobulins to the microbiota can vary. For gut microbiota, low affinity is likely characteristic. This is necessary so that the microbiota also participates in the absorption of food.

Avidity of immunoglobulins

1. Each triumvirate of the clinical attractor regulates the tissues and organs under its control. However, these tissues and organs can sometimes affect other triumvirates of other clinical attractors. The appearance of clinical symptoms and diseases occurs in the following cases
2. The avidity of immunoglobulins to the microbiota changes. Secretory immunoglobulins are located on mucous membranes. Each microbiota of a clinical attractor is characterized by a certain degree of binding of the secretory

immunoglobulin to the antigen. The degree of binding (affinity) can be either weaker or stronger. In either case, symptoms of diseases or the diseases themselves may appear

For a clinical attractor, a certain type of immunoglobulin may be characteristic. Can you imagine how many possible interactions there are between microbiota and immunoglobulins?

Immunoglobulins are produced for each of these microbiotas. These immunoglobulins are found both on the epithelial cells of the microbiota and circulating in the blood. Thus, the blood contains a whole set of all immunoglobulins. We do not know which of them are responsible for which microbiota. Besides, there are immunoglobulins against various viruses and other bacteria with which the organism has come into contact. This is schematically represented in the drawing (Figure. 5).

Each triumvirate of the clinical attractor regulates the tissues and organs under its control. A change in the balance at the level of the triumvirate can lead to the appearance of certain clinical symptoms and diseases in the tissues and organs under the control of this attractor. Interestingly, the condition of other organs under the control of this attractor improves. For example, with a stomach ulcer (gut attractor), there are usually no serious brain diseases (tumors, Alzheimer's disease), and vice versa."

Relationship between humoral and secretory immunoglobulins

Immunoglobulins circulating in the blood indeed play a crucial role in our immune response. Most of these immunoglobulins are produced in response to our microbiota, especially on mucous membranes.

Secretory Immunoglobulin A is the predominant mucosal antibody, which binds pathogens and commensal microbes. SIgA is a polymeric antibody, typically containing two copies of IgA that assemble with one joining chain to form dimeric IgA that is bound by the polymeric Ig-receptor ectodomain, called secretory component.⁶⁷

In normal conditions, secretory immunoglobulin A (SIgA) is the principal antibody produced by B cells in the GIT mucosa.⁶⁸

IgA is the most dominant immunoglobulin class in humans. IgA-producing cells are mainly distributed in the mucosa lining tissues such as the intestine and oral and nasal cavities.⁶⁹ But there can also be IgG immunoglobulins.⁷⁰

Secretory immunoglobulins A (sIgA) and humoral immunoglobulins A (IgA) are closely related. IgA in the blood is primarily in monomer form and can penetrate mucous membranes. Once there, they transform into sIgA by binding with the secretory component, which helps IgA move through epithelial cells and stabilizes it on the surface of mucous membranes.⁷¹

Thus, humoral IgA produced in response to microbiota can convert into sIgA, playing a crucial role in protecting mucous membranes from pathogens. The connection between them lies in their common origin and functional transformation, providing an effective immune response both in the bloodstream and on mucous surfaces.⁷²

When the antigenic composition of the microbiota changes, it primarily affects the humoral immunoglobulins A (IgA) in the blood. Then the information about the changes is transmitted to secretory immunoglobulins A (sIgA), which are located on mucous membranes and have a more direct contact with the microbiota. Thus, the changes start with humoral immunoglobulins and then are passed on to secretory ones.

To further advance our understanding in the field of immunology, it is essential to conduct scientific studies aimed at identifying and thoroughly describing the mechanisms of interaction between humoral and secretory immunoglobulins of class A. This will help elucidate their relationship and coordinated involvement in the body's immune defense.

Interaction between ocular microbiota and gut microbiota

How can gut microbiota cause dry eye syndrome,³⁷ and glaucoma⁷³ or AMD?^{74,75}

Consider this with the example of the epithelial cells of the conjunctiva and cornea. A tear film is present on their surface. This film contains ocular microbiota.⁷⁶

Therefore, MHC-1 cells of the conjunctiva contain antigenic determinants of ocular microbiota in the form of peptides. But, since the evolutionary development of the eye arose in coelenterates, some MHC-1 cells of the conjunctiva may contain antigenic determinants of gut microbiota in the form of peptides. Therefore, regulation occurs from two different microbiota.

Disturbances in nutrition or competition between microbes in the gastrointestinal tract for resources can lead to an imbalance between the gut microbiota and the surrounding immunoglobulins (changes in the avidity of immunoglobulins with antigens). A disturbance in the antigen composition of the gut microbiota will immediately lead to a change in the antigenic determinant present on the MHC-1 cells of the conjunctiva. This can change the local immunological status and lead to the appearance of symptoms of conjunctivitis or dry eye syndrome (Figure.7)

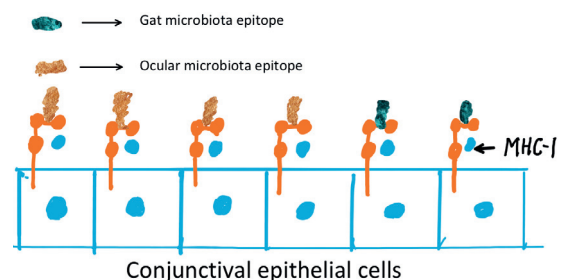


Figure 7. MHC-1 cells of the conjunctiva contain antigenic determinants of ocular microbiota in the form of peptides. However, since the evolutionary development of the eye arose in coelenterates, some MHC-1 cells of the conjunctiva may contain antigenic determinants of gut microbiota in the form of peptides.

Optic nerve and optic tract

The ocular attractor regulates the condition of the conjunctiva, the anterior segment of the eye, and the optic nerve, optic tract, and adjacent neurons. The optic nerve and optic tract are also regulated solely by ocular microbiota. This is confirmed by the fact that in the treatment of optic nerve atrophy using the new HAT Medicine method, with the help of minimal antibacterial drugs aimed at partially suppressing the ocular microbiota, there is an improvement in visual acuity and visual fields in all cases.⁷⁷

This occurs regardless of the cause of optic nerve atrophy (trauma, tumor, glaucomatous atrophy, provided normal intraocular pressure). When treating young patients with optic nerve atrophy and associated neurological disorders using the new method, children's muscle tone improves dramatically, they become more active, and neurological symptoms decrease (Figure. 8).⁷⁸



Figure 8. The optic nerve and optic tract are regulated by the ocular microbiota. The ocular microbiota is also responsible for the areas of the brain located near the optic tract.

Therefore, MHC-1 of the neurons of the visual pathway, oligodendroglia covering the nerve, and brain cells located near the visual tract are connected to the epitope peptide (antigenic determinant) of the ocular microbiota.

By normalizing the balance between ocular microbiota and the surrounding immunoglobulins, it is possible to achieve remission of optic nerve atrophy and improvement of visual functions.

It is possible that in some cells surrounding neurons, MHC-1 relates to the peptide determinant of the genitourinary tract microbiota. This assumption is because optic neuritis often occurs in women after menstrual cycle disturbances or genitourinary tract diseases.^{79,80,81}

Conclusions

From the new perspective of Chaos, the emergence of all human diseases, particularly eye diseases, is considered.

All cells in the body are arranged in the form of fractals. In diseases, the fractal structure of cell arrangement is disrupted.

The basis for the emergence of diseases and the disruption of the fractal structure of cells lies in the imbalance between the epithelial cells of humans that come into contact with the external environment, the microbiota, and the surrounding immunoglobulins. This symbiosis between mucosal cells, microbiota, and immunoglobulins is called the "triumvirate," by analogy with ancient Roman history.

This triumvirate regulates all organs and tissues of the body. This entire system represents a "clinical attractor." The term "clinical attractor" reflects the idea of a self-sustaining system where interactions between the microbiota, mucosal membranes, and surrounding antibodies regulate various tissues in the body.

There are five clinical attractors in the body: gut attractor, urogenital attractor, respiratory attractor, ocular attractor, and aural attractor.

It is hypothesized that peptides on the surface of MHC-1 of somatic cells are epitopes of the microbiota. Each cell of an organ or tissue in the human body has MHC-1 on its surface, which is an epitope of a specific microbiota. The specific antigenic determinant of the microbiota on the cells of the conjunctiva, choroid, and retina

depends on the evolutionary history of that specific tissue.

For example, a peptide associated with MHC-1 cells of the optic nerve and visual tract is characteristic of the ocular microbiota. Restoring the balance between the ocular microbiota and the surrounding antibodies can stop the progression and improve the visual functions of patients with optic nerve atrophy.

This theory provides a new perspective on the origin and treatment of all human diseases.

Ethics

Peer-review: Externally peer-reviewed.

Conflict of Interest:

No conflict of interest was declared by the author.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Study association

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CORRECTIONS

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The Ophthalmology Cases & Hypotheses (OCH) accepts original research articles, review articles, case reports, hypotheses, clinical images, short commentary, letters to the Editor, and Medical Ethics on Eye Related Researches on all the aspects of ophthalmology and eye diseases. This journal publishes the study related to Strabismus, Amblyopia (Lazy Eye), Astigmatism, Blepharitis, Cataracts, CMV Retinitis, Conjunctivitis (Pink Eye), Corneal Ulcer, Detached Retina, Diabetic Retinopathy, Diplopia (Double Vision), Glaucoma, Optic atrophy, Uveitis, Macular Degeneration (AMD), Macular Dystrophy, Ocular Migraine, Ophthalmology, Ptosis (Drooping Eyelid), Retinitis Pigmentosa, Eye disorder in Pregnancy, Uveitis and other eye diseases.

Submissions shall be clear, concise, and well-documented reports. Submissions on specific themes are welcomed for publishing in this esteemed Journal. Published manuscripts should have not been accepted or will not be published elsewhere. Manuscripts should be devoid of any ethical problems or malpractice. The paper should be unique and not published elsewhere (except in conference abstracts). All authors should read and approve the authorship responsibility and publication ethics principles presented at our website. All authors further warrant that the undersigned are the sole authors of this work. One author has been entitled as the corresponding author with contact details and postal address. Only papers written in English are considered. The articles should be comprehensible to a reader who is fluent in English and should be edited prior to submission to ensure that standard English grammar and usage are observed.

Article type

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Each type of publication is defined as follows:

1. Cases Reports
2. Research Article
3. Review Article
4. Clinical Image Article
5. Short Commentary
6. Hypotheses
7. Medical Ethics on Eye Related Researches
8. Letter to Editor etc.

The research articles should be 4–10 pages, and the review articles should be no more than 12 pages.

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Manuscript Titles: Title should be brief and accurate technical enough to explain the content it holds in the manuscript.

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Original articles: Should contain a structured abstract, 3-5 keywords, introduction, methods, results, discussion, conclusion, ethical declaration, acknowledgment, funding, and references. There is no restriction on word numbers and supporting documents. RCTs should be registered at any RCT Registries approved by the WHO.

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Abstract, not less than 250 words, structural, concise, and comprehensible to readers. Keywords are used for indexing purposes; three to five keywords should be selected

Introduction should cover a short background of former studies and potential gaps in the literature, and specify the aim of the study.

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Discussion should challenge the outcomes of the research with other publications in the literature in the format of arguments and counterarguments. The limitations and strengths of the study and the implications of the findings for future study or clinical practice should be presented.

Conclusion should present the final outcome and brief recommendations that have been reached.

Ethical declaration consists of ethical approval and conflict of interest that should be presented and reported.

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Clinical images are the pictures that show the clinical findings of a particular case of the patient. The clinical pictures should include questions and answers that should educate or remind readers about an important clinical situation or event. The image should not just describe the picture; however, should be informative enough from a clinical teaching view.

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Bakı, Az1122, Zərdabi pr. 78c
Tel: 012/070 4977021
E-poçtu: info@ave.az

