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A new model for chronic diseases

S.D. Sara Diani

Independent Researcher, Lahnstein, Germany

A B S T R A C T

Chronic diseases are defined diseases whose symptoms last for at least six months and tend to worsen over time. In Europe, they cause at least 86% of deaths.

In this speculative unifying model I set a new hypothesis for the etiology of the majority of chronic diseases. The main aim is to put order and observe our organism in a systemic way, connecting pathologies we now see as disconnected phenomena, with the conceptual frameworks of complex systems and network medicine.

Chronic diseases could be caused by a first unsolved acute infection. In case the pathogen cannot be completely eliminated, it becomes a persistent infectious. After the acute episode, some mild symptoms will occur and probably disappear; the chronic disease will remain latent over time. It will manifest even after years or decades, in the presence of another acute infection, a particular stress, trauma, or another event. The presence of the persistent infectious elicits changes in the immune and systemic regulation, and these processes degenerate over time. They will assume their rules and patterns, being independent from the initial stimulus. The key to understand the dynamics and individuality of chronic diseases is the immune system and its networks. The immune mechanisms that can lead to the persistent response are mainly the switch from the Th1 to the Th2 immunity and the molecular mimicry.

The first persistent infectious will also modify the susceptibility to other pathogens, facilitating new infections and new consequent persistent infectious.

From the immune point of view, our organism is divided into three compartments: the outer one, which comprehend all the surfaces in contact with the environment, the intermediate one, which comprehend the internal organs and tissues, and the innermost one, comprehending the Central Nervous System and the adluminal compartment of the seminiferous tubule. The immune key-role is played respectively by the mucosa-associated lymphoid tissue, the endothelium, the blood–brain barrier and blood-testis barrier. The chronic diseases follow a progressive scheme, involving the three compartments from the outer to the innermost one.

The primer microorganism at the origin of the majority of diseases could be streptococcus, or staphylococcus. Both cause acute in children, with a great variability of responses and symptoms, and both cause molecular mimicry.

This model can be tested and proved in more ways, I propose here some of them.

It could pave the way to a radical change in our comprehension and therapeutic approaches to chronic diseases.

Introduction

Chronic diseases are diseases whose symptoms last for at least six months and tend to worsen over time. The aggravation occurs constantly, or alternating stable phases with worsening ones. Usually chronic diseases occur in young people, lie latent for years or decades, and only materialize later. Currently the OMS defines them as non-infective diseases. Although there is no single unambiguous and universally accepted definition, everyone agrees on one fundamental factor: chronic diseases result from multiple causes linked together. The new scientific evidences show always more diseases co-caused by microorganisms (for example [1–8]). I'm going to put order and to show a consistent way to interpret and rationalize these results.

In Europe, chronic diseases cause at least 86% of deaths [9], therefore this is a crucial theme. In order to achieve a better therapeutic perspective and a more effective and targeted prevention, we need to better understand how they are structured, their characteristics and what are the most important predisposing factors.

The conceptual framework of this model, which wants to be systemic, are complex systems [10]. Through this frame I introduce the model. In particular the most important nodes of the immune dynamics, and the main mechanisms related to the systemic degeneration over

E-mail address: info@saradiani.com.

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time will be explained. In fact we are a complex system, and so we respond to stimuli with a new organization and systemic restructuring. This process results in the creation of a response network after encountering new information. The network approach is essential, and it is necessary especially at the immunological and nervous level. Understand which immune networks are activated in different pathologies is one of the keys to change the approach to chronic diseases, and more.

In this paper I will use in an equivalent manner words like *stimulus*, *agent*, *information*.

The persistent infectious and the model premises

The mechanism "encounter with a pathogen → new response network → symptoms" is a possible pattern in acute diseases [11]. What about in chronic ones?

In chronic we can only speculate a unique disease model. The great variety of possible changes seems an obstacle to genuine understanding of each single change at the origin of all the structural changes which become manifest through the observable symptoms. The model is derived from a new interpretation that A. Micozzi and P. Benedetti gave to the book "Chronic diseases" by Hahnemann [12].

We can assume that, as in the acute illness, even in chronic diseases occurs a network response to an initial stimulus. There is a big difference between acute and chronic diseases: in the acute illness, the information is eliminated by the organism. In the chronic one, the pathogen stimulus remains within the organism. It becomes persistent in the body, and unleashes as a result a continuous and degenerative response. This is the heart of the vision, and must be verified through in-depth study of the immune system and its networks.

In chronic diseases there is an etiologic agent: the information that can't be eliminated. For example, it can be a particularly insidious pathogen, or one that produces toxins, or that has cell tropism as occurs for viruses. Furthermore, there are other pathogenetic co-responsible factors, such as the predisposition and the state of the organism at the moment when it comes into contact with the pathogen. These two factors will change:

- susceptibility (the chance to know certain information and react against it to remove it, in case it's pathogenic)
- the type of acute response (which can be effective or not),
- possible support for the disease, or the likelihood of degenerative changes of the chronic network.

An infection takes place, and this can also happen in the early stages of life. Due to the combination of the three fundamental factors, namely the characteristics of this microorganism, the predisposition and the system state at the time of infection, this information can't be deleted. It becomes what we might call a *persistent infectious*. This triggers a series of processes that may underlie most chronic diseases that so far we have considered as different and distinct phenomena. Surely there are many differences between the various networks that can be opened in chronic, but the underlying mechanisms may be common.

Persistent infectious is the new fundamental knowledge, which makes us understand why we lose systemic coherence. It's the coupling between the system and the persistent infectious which gives rise and maintains the pathological and degenerative processes that characterize chronic diseases for a lifetime.

The currently available therapies allow for some time to control the pathogenic processes. But always, after a certain amount of time, a drug alone is no longer enough, the symptoms and the signs reappear with the same power or with even a greater force, and another drug therapy is the only viable option.

For example, is common in hypertension to add antihypertensive during time. There are specific guidelines that indicate the suitable therapeutic combinations for the different patients' classes [13,14].

Otherwise, the disease in a given district remains controlled, but may appear in other organs/districts/systems.

This happens for examples with cancer. Metastasis can involve other districts, even after years.

Currently it is thought that these are different diseases, but the truth is that they are different manifestations of the same problem, which occurs at the level of systemic and immune regulation. In fact, according to this new model, the new symptom picture can be related to those that appeared earlier. In other words, the new manifestation can be an indirect consequence of the first ones.

Thus, the chronic disease is a regressive spiral, due to deterioration in the systemic capacity to respond in an adequate, effective, optimized and ordered way to different stimuli. It causes a continuous and sustained increase in entropy.

In this logic, we see that there isn't a clear direct cause-effect mechanism, but there are a number of networks that are activated, modulated and which influence each other in mutual synergy.

The presence of persistent infectious modulates the body's response system activated by following information. Independent recursive systemic processes begin from the initial pathogen stimulus and that is self-maintained over time, because they become the lower-entropy solution for the system [15].

A new "coupling" between the new response networks and all other active systemic begins. These two entities influence each other, and this gradually leads to disorder. Once triggered, this network of chronic pathological response will have a negative effect on all other regulatory networks of the system, and this will cause other diseases. Dysfunctions in the regulatory networks occur [16]. Consequently, the body will not be able to know and react optimally to the subsequent information.

During life, the response is given by a series of assisted bifurcations. It's a phenomenon of the same nature of what Waddington Hal Conrad studied in inductions of embryological development: evolutionary and peaceful growth alternate [17]. The new states of the system are in fact evolutionary bifurcations, i.e. they are discrete changes. They either happen or do not happen. This affects the chronic diseases because in the pathological progression alternate phases in which the disease is in a latent phase, in which it remains silent and is expressed (if it does) with mild and not very specific symptoms, and phases in which the disease manifests itself, or worsens.

After an exacerbating factor such as stress, trauma, surgery, the appearance of a particular pain, a change in lifestyle, an acute infection or an acute illness, the disease is made manifest, and the symptoms become more intense. These forks can also bring the acute disease on chronic, or to a further exacerbation of chronic disease in one or more specific districts.

If we introduce the idea of persistent infectious, we must consider the immune system (along with the nervous system that allows the dissemination of information and also reports to the central level), the protagonist of chronic diseases. It's the immune system activated and continuously triggered by pathogen that causes and allows the progression of the disease.

Immune mechanisms underlying the persistent infectious

On the immune level, the great variability of response and chronicity after a single or a few initial stimuli (epitopes of microorganisms or other antigens) can be explained by several mechanisms:

- Certain bacteria and viruses can trigger multiple responses and diseases within the system. This happens for example with Streptococcus, or Helicobacter pylori. The model a microorganism - a disease does not always work and is only partial.
- The individuality of the immune response. This is defined before at the genetic level, then at the epigenetic one. It is based on the polymorphism, on the genotypic and phenotypic diversity of individuals of the same species [18–21].
- Molecular mimicry [22]. It's a strategy used by microorganisms to