



Chronic infections: causes and possible approach to treatment

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Abstract

The mechanisms of chronic infectious diseases remain poorly understood, and optimal methods for their treatment are still to be found. An attempt is made to analyze available data by analogy with natural chronic foci of normal microflora, which are useful and even necessary to the host. The analogy is justified because both normal and pathogenic infective microfloras are basically similar in their essential characteristics, such as contagiousness, conditional pathogenicity, the possibility of healthy carriage, and chronic persistence in the host body. On this basis, it is assumed that foci of any persistent microflora are formed because they are necessary for the host, which explains the difficulty of curing chronic infections. Alternative ways of their treatment are discussed.

Keywords: Chronic infection, infectivity, contagiousness, normal microflora, active susceptibility

Introduction

Recent advances in microbiology, infectology, and other sciences lead to understanding that our views on the biological meaning of interaction between infective microorganisms and susceptible host species should be revised. We habitually consider microbes to be our enemies, which is only natural as they cause diseases, some of them lethal. This is often regarded as the struggle for existence in terms of Darwin's evolutionary theory.

However, first, Darwin spoke of the competitive "struggle for existence" metaphorically, not meaning that the competitors inflict direct harm to one another. He spoke about organisms' acquiring evolutionary novelties that allow them to escape competition and occupy a vacant ecological niche (if we may use the modern term).

Second, microorganisms by no means could be called competitors of metazoans, their needs being too different.

Third, and most important, microorganisms have no biological reason for pathogenicity: they live on nutrients contained in the host body, but they die if the host dies from illness. Hence, pathogenicity even decreases the microorganisms' fitness and could not be an evolutionarily determined character.

The subdivision of microfloras into "normal" and "pathogenic" is not based on any objective criterion. Not only "pathogenic," but also "normal" microorganisms may exhibit pathogenicity, which has been repeatedly noted both in the past century

and at present [1].

At the same time, healthy carriage is more characteristic of "normal" microorganisms than pathogenicity. Furthermore, healthy carriage of infective pathogenic bacteria is found increasingly often. According to some authors, healthy or asymptomatic carriage of contagious microorganisms is more frequent than infectious diseases [2]. The active susceptibility concept [3] holds that precisely healthy carriage is the normal relationship between infective microorganisms and susceptible species. For example, thousands of healthy carriers of the cholera pathogen live unharmed in India [4-7]. Healthy carriers of the tuberculosis, typhus, gonorrhoea, syphilis, and plague pathogens [8,9] are also not rare. Generally, pathogenicity looks more like an exception than a rule. Therefore, pathogenicity cannot serve as a criterion for classification of microorganisms, nor can it be an advantageous trait that they have developed in the course of evolution. Infectivity is a stricter classification criterion in this case, because infectivity, in contrast to pathogenicity, is determined by species-specific characteristics of both microorganisms and susceptible species.

Chronic infections and infectivity

Chronic infections are a major concern for public health. The difficulty of controlling them would have been easier to understand had microorganisms from chronic foci displayed

a high antibiotic resistance, or had immune deficiencies been invariably found in patients with chronic infections. However, there are many cases of chronic infections where the pathogens are sensitive to antibiotics and the immune system is normal [10-13,16-22].

It is true that antibiotic-resistant bacteria have also often been found in chronic infection foci; in addition, the protective effect of biofilms characteristic of chronic infections is well known. This might explain why chronic infections are difficult to treat, but not why their primary foci are formed in the host body. Some infectious diseases (syphilis, frambesia, pinta disease, ozena, rhinoscleroma, leprosy, tuberculosis, mycobacterioses, etc.) are intrinsically chronic; i.e., they are chronic from the onset in all patients, irrespective of the resistance of their pathogens to antimicrobials.

Probably, the causes of chronic infections and their resistance to treatment will become clearer if we try to relate the formation of their foci with the primary cause of infectivity in terms of the active susceptibility concept [3].

Note that infections whose pathogens are non-contagious, i.e., not transmitted from human to human (e.g., tetanus, botulism, and gas gangrene) never take a chronic form. In other words, only contagious microorganisms cause chronic infections. The normal microflora is the most contagious: all representatives of a given species are infected with it shortly after birth, because it is permanently necessary for the host.

Therefore, determining the cause of contagiousness seems crucial for understanding chronic infections.

In this regard, of special interest are natural foci of chronic infection formed by infective normal microflora in healthy human and animal bodies. Obviously, the normal microflora is infective and contagious and chronically persists in the host body because it is necessary for the host: "normal" microorganisms are involved in food digestion, including the cleavage of proteins and carbohydrates, as well as absorption of nutrients and synthesis of vitamins. The normal microflora stimulates immunity, directing its protective activity against pathogenic bacteria. It also directly suppresses the reproduction of some pathogenic microorganisms. Precisely these useful microorganisms form natural foci of chronic non-pathogenic infection. These and other useful functions make it necessary that the host body be chronically infected with the normal microflora.

Thus, it is not that "microbes infect us," but rather that we "infect ourselves" with our normal microflora right after birth, which I refer to as active susceptibility [3]. Its contagiousness is our necessity. So, microorganisms' contagiousness and infectivity are in essence the capacity of the host body for attracting the microflora that it needs, rather than a property of the microorganisms themselves.

The contagiousness of prions is indirect but important evidence in favor of an active role of the host body in infection. While pathogenic microorganisms are commonly believed to force their way into the host body "to struggle for life," which

could explain their infectivity and contagiousness, prions are not organisms, and this explanation of contagiousness is inapplicable to them. Prions are merely protein molecules, whose "fitness" is fitness for functioning rather than adaptation for survival. Infectivity of prions and susceptibility to them are explainable only by active involvement of prions in the host's metabolism on the host's own "initiative." Pathological prions (PrPsc) are isoforms of normal intracellular protein prions (PrPc); i.e., PrPsc and PrPc are very similar to each other [23]. Therefore, a macroorganism actively involves pathological prions, along with normal ones, into its metabolism.

The issue of contagiousness entails an important question: What is the fundamental difference between a "normal" microflora and "pathogenic" microorganisms? Obviously, there is no essential difference between them: both of them are infective, and both may be pathogens of infectious diseases or, alternatively, merely persist in a healthy carrier. Chronic infection and epidemics are also characteristic of both "normal" and "pathogenic" infective microfloras. In fact, the largest "epidemic," which will never end, is caused by normal microflora. Since chronization of the infection with the "normal" microflora results from its permanent necessity for the host, then, given the essential similarity between the normal and pathogenic microfloras, it is conceivable that chronic pathogenic infection foci are also formed because the host needs them.

This assumption might seem absurd at first glance. What benefit could be expected from microbes causing illness? However, first, "normal" microorganisms also sometimes cause diseases; second, "pathogenic" ones not always cause them and may be useful to a healthy carrier. Indeed, there is a growing body of evidence that many infective, contagious "pathogenic" microorganisms are useful under the conditions of healthy or asymptomatic carriage.

It is believed that endogenous retroviruses were common exogenous viruses in the evolutionary past, and they often caused outbursts of diseases in susceptible species. At present, these viruses or, to be precise, their genes constitute a noticeable proportion of the human, animal, and plant genomes, where they serve as transposable elements [25].

There is evidence that retroviral genes in the tobacco genome take part in antiviral defense. The loss or dysfunction of some genes of endogenous retroviruses expressed in the sheep placenta disturbs the formation of placenta and leads to miscarriage. Note that the dysfunction, rather than the function, of endogenous retrovirus genes leads to pathology. It is assumed that the very origin of placental mammals is a result of coevolution of animals and retroviruses [25-28].

Mycobacteria, lymphocytic choriomeningitis virus, filariae, and schistosomes have been found to prevent diabetes mellitus in inbred mice [29]. Extracts from streptococci and klebsiellae injected along with Freund's complete adjuvant have a similar protective effect [30-32]. Mycobacteria can prevent autoimmune encephalomyelitis in experimental animals [33].

These and similar data have led to the hygiene hypothesis, which relates the recently increasing incidence of non-infectious (allergic, autoimmune, and some other) somatic diseases with the overuse of hygienic measures aimed at almost complete extermination of microorganisms in our close environment [34,35]. Recent studies on Alzheimer's disease rate have yielded conclusive evidence for this concept. The decrease in microbial load has proved to be related with the increase in Alzheimer's disease incidence [36].

Thus, any infective and contagious microorganisms, "normal" or "pathogenic," may be both useful and harmful. Since multicellular organisms are actively susceptible to the normal microflora because its useful properties are necessary for the host, despite that the same microorganisms may cause diseases, we should conclude that chronic foci of "pathogenic" microorganisms are also formed because the host needs them. It is clear that, if a natural phenomenon has harmful aspects, this does not mean that it is essentially harmful. There is a growing understanding that existence of infectious diseases does not mean that contagious microorganisms are there to do harm to susceptible species. Contagious microorganisms may, under different conditions, either fulfill useful functions in the host body or cause disease, as is the case with normal microflora. However, precisely the necessity of their useful functions for the host determines the active susceptibility to microorganisms. Their contagiousness rather than pathogenicity is a species-specific character of both microorganisms and susceptible host species. The fact that contagiousness is a permanent integral part of interspecific relationships indicates its evolutionary rather than accidental origin and suggests that it is necessary for both the microorganisms and the host.

Contagiousness is actually the host body's capacity for involving microorganisms in its vital functions (active susceptibility), rather than a property of the microorganisms. However, there is also passive susceptibility, e.g., the aforementioned susceptibility of humans to tetanus, botulism, and gas gangrene pathogens. These microorganisms accidentally penetrate into the human body, which appears to be a good nutrient medium for them. For active susceptibility, a suitable set of nutrients in the host body is not enough; many pathogenic bacteria grow on nutrient media prepared from tissues of animals in which they never cause diseases under natural conditions. For example, cholera vibrios grow on beef broth, but cattle never have cholera. For a host to become susceptible to microorganisms, certain activity on the part of the host body is required; i.e., a microorganism's contagiousness is a direct consequence of the host's active susceptibility. This is why non-contagious microorganisms may accidentally infect the human body but do not cause chronic infections.

There are apparent exceptions to this rule. For example, uropathogenic *Escherichia coli* (UPEC), which sometimes cause chronic urinary tract infections, is not contagious.

This can be explained as follows. Since contagiousness

is primarily necessary to, and determined by, the host, an infection is not transmitted unless there an actively susceptible individual in the near environment. However, active susceptibility is likely to vary both in different species and in different individuals within a species. The interspecific variation is expressed in that different species have normal microfloras of different compositions. The individual variation may consist in that individuals differ from one another in the degree of active susceptibility, some of them being practically unsusceptible to a given pathogen: even during severe epidemics, not all persons closely contacting a patient become infected. Active susceptibility may also change in the course of ontogeny. It is known that children under one year of age, whose immune system is still immature, rarely have cholera [10]. These considerations suggest that a population-wide enhancement of the active susceptibility to certain microorganisms as a result of changes in the environmental conditions is one of the main prerequisites of an epidemic.

We can assume that active susceptibility to UPEC does occur in the human populations, but it is rather rare because this microorganism is necessary for only some humans with specific individual characteristics. In some of them, UPEC causes chronic infection. However, since the population frequency of UPEC susceptibility is low, the disease is hardly ever transmitted from human to human; i.e., it is non-contagious.

In summary, the above considerations lead to the understand that a pathogenic infective microbe may be both an "enemy" and a "friend." Normally, all infective microorganisms serve useful functions in the host, and this is why they are infective in the first place. Disturbance of these normal, evolutionarily determined interactions between infective microorganisms and their hosts leads to infectious diseases.

Practical implications

Thus, the necessity of chronic infection foci for the host body is the probable reason why the diseases caused by them are so difficult to cure. Even if a natural chronic infection focus is eliminated, the host will "infect itself" with the same microorganisms again because it still needs them. This can be exemplified by germ-free animals born and raised under sterile conditions and lacking the normal microflora. When transferred to the normal environment, these animals are immediately infected with the necessary microorganisms. It is conceivable that this is also the case with the treatment of chronic infections: if antibacterial treatment kills all microorganisms in an infection focus (which it probably does), the patient will soon become re-infected. This is why chronic infections defy cure. Not knowing this, we regard this failure of anti-infection therapy as evidence that, for some reasons, there is no way to handle chronic infections. However, the above considerations allow us to suggest other approaches to treatment. As mentioned above, some researchers believe that endogenous retroviruses used to be common exogenous viruses in the remote past. Since interactions with them often results

in outbreaks of viral diseases, evolution took the course of including the necessary genes of these viruses into the genome of the multicellular hosts; these genes are now called endogenous retroviral genes. As for bacteria, many human genes exhibit obvious similarity with bacterial genes [37]. In this way, wise Nature has “killed two birds with one stone”: on the one hand, susceptible species have received what they need from viruses and bacteria; on the other hand, these species have got rid of the active susceptibility to these microorganisms and, hence, of the diseases caused by them. In theory, if we managed, following Nature’s suit, to integrate certain genes of microorganisms that form a chronic infection focus into the patient’s genome, the active susceptibility to this infection would have to disappear, and the infection focus could be eliminated with standard antibiotic treatment. We might even do without transgenic manipulations in treating human and animal chronic infections. The body eventually needs the products of certain microbial genes rather than the genes themselves. Hence, these products could be isolated and used as drugs. The application for a patent on the novel method for preventing infectious diseases has been published by the World Intellectual Property Organization; however, the method has not yet been developed experimentally [38,39].

Conclusions

The above considerations could explain the causes of chronic infections and show new approaches to their treatment by integrating certain microbial genes into the patient’s genome or administering the products of these genes into the body. At the current state of medicine, with antibiotic resistance being widespread, the search for new approaches to treating infectious diseases is an important task. However, the approach suggested here raises many questions that should be answered before its practical implementation. What are exactly the useful functions of the chronic foci of “pathogenic” microflora in the host body? Why, unlike the genes of endogenous retroviruses, have the genes of modern exogenous pathogens not been transferred into the genomes of susceptible species? Which factors promote the transformation of healthy carriage into an infectious disease? Which microbial genes should be integrated into the host genome, and into the genome of which cells exactly? How are we to do this? Apparently, this list of unanswered questions is far from complete. There are grounds to believe, however, that coordinated research in the areas mentioned above will eventually allow us to reasonably handle infection processes, which, on the one hand, are necessary for the susceptible species but, on the other hand, cause illness if they come out of control. This work will undoubtedly take much effort and require participation of more than one research team. I hope that this paper will be a step towards finding potential participants in such a collaboration, where we could gain fundamental knowledge as well as develop medical applications.

Competing interests

The author declares that he has no competing interests.

Acknowledgement

I am grateful to Prof. V.M. Boev, Prof. A.I. Smolyagin and V.L. Ushakov for their help in preparing this paper.

Publication history

Editors: Triveni Krishnan, National Institute of Cholera and Enteric Diseases, India.

Daniel Hubert Darius J, Johns Hopkins School of Medicine, USA.

ELC: Ishtiaq Qadri, King Abdul Aziz University, Saudi Arabia.

Received: 21-May-2014 Final Revised: 22-Jul-2014

Accepted: 25-Jul-2014 Published: 08-Aug-2014

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Citation:

Malyshkin AP. **Chronic infections: causes and possible approach to treatment.** *Res J Infect Dis.* 2014; **2**:3.
<http://dx.doi.org/10.7243/2052-5958-2-3>