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Special Article

Pathogens as Living Things

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INTRODUCTION

Infectious diseases have recently become a common subject in the mass media. Because the organisms causing infectious diseases are too small to be seen with the naked eye, we fear them as if they were ghosts. Furthermore, we may have trouble thinking of these organisms as living things.

Pathogens are living things, but many people think they are strange and hate them. Most organisms live with a common principle : "the environment is indispensable for survival." Such organisms never sever their connection with their environments. In medical terms, however, pathogens seem to neglect or abuse their environments or hosts. Ironically, human beings do much the same thing. We can see a great similarity between the deaths of human beings by pathogens and the destruction of nature by human beings. In this way, human beings and the pathogens they hate might have similar relations to their environments.

This similarity is a big surprise. Many human beings regard themselves as typical living things. But this assumption is false because humans neglect their environment.

Humans are destroying the natural environment ; this is as foolish as trying to break the legs of chair you're sitting on. Pathogens might be similarly foolish because they destroy their environments, which are their hosts.

But both human beings and pathogens seem to enjoy their prosperity despite their destructive behavior. Perhaps the principle that their environments are indispensable does not apply to them?

Environments might be classified as true ones and false ones. Every living thing should have a harmonious relationship with its true environment simply because only a true environment stably supports a long life. Consequently, no living thing, including human beings and pathogens, should destroy its true environment.

Does this mean that not even pathogens should destroy their true environment?

Yes. Even plague bacilli never kill their true hosts, which are wild fleas that live on rats. Neither rats nor humans are the true hosts of plague bacilli. Plague bacilli cannot have a harmonious relationship with humans or rats. Therefore, plague bacilli are not pathogenic for fleas but are pathogenic for humans and rats.

What about the destructive behavior of human beings?

In the same way, the likely reason human beings are destroying the natural environment is that it is not their true environment. The hypothesis that the true environment of humans is not the natural environment but rather the human body itself is explained in this paper.

The relations between humans and pathogens and between nature and humans will be discussed in parallel with the host-parasite relationship in this paper.

Understanding is possible only through an analogy when no direct experience is available. Various pathogens might be the best model to understand the behavior of human beings.

THE ENVIRONMENTS OF PATHOGENS AND HUMAN BEINGS

1. Living things ignoring the principle that "the environment is indispensable"

Most people know that infectious diseases are caused

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by microscopic organisms called microbes. Most microbes are harmless, and some are even beneficial to humans. In terms of the number of species, pathogenic microbes (pathogens) are a minority.

What is the difference between pathogens and other microbes? Pathogens seem to neglect their environment, namely, the human host. Humans occasionally die of infectious diseases. When their human host is killed, pathogens would appear to lose their environment. Such pathogens seem to argue against the principle that every living thing needs its environment to survive.

Human beings are also engaged in the destruction of natural environments everywhere on Earth. The death of human beings by pathogens and the death of nature by human beings might share a similar host–parasite relationship.

Furthermore, diabetes mellitus caused by overeating might be similar to the destruction of nature through the activities of human beings. In this case, the human body might be considered the environment of the human mind.

Both pathogens and human beings are paradoxically useful for more precisely verifying the principle that the environment is indispensable for all life and for more deeply understanding the relationship between life and environment.

It is highly doubtful that epidemics of infectious diseases and large-scale changes in the natural environment made by humans reflect the prosperity of pathogens and human beings. The continuous destruction of the environment might represent the prosperity of the corresponding organism if the environment were indestructible. Every environment, however, should be considered vulnerable to damage or destruction. "What is the prosperity of living things?" is a main subject of this paper.

2. *Origin of the host–parasite relationship*

Bacteria are representative microbes and can be classified as parasitic or saprophytic in respect to their environment. Organisms that are the environment for parasitic bacteria are called "hosts." Saprophytic bacteria live in the soil and in water. They have no direct host, although they live on waste supplied by various other living things. Consequently, both parasites and saprophytes are parasitic in a broader sense.

Some parasitic bacteria have a host–parasite relationship with humans, and some of them are pathogenic. Most saprophytic bacteria are not pathogenic to humans because they do not have a host–parasite relationship with humans. Some saprophytic bacteria, however, are highly pathogenic to humans. Examples of pathogenic bacteria are tetanus bacilli and botulinus bacilli.

In the host–parasite relationship, the host plays the role of the environment for the parasite, and the host is a parasite of the natural environment. Furthermore, bacteria serve as hosts for bacteriophages or phages, which are viruses. Viruses are, of course, important pathogenic microorganisms. Phages don't have a direct host–parasite relationship with humans.

We see here a structure like that of Russian nesting dolls, or matreshka. The nested structure will be an important concept in this paper when we consider the pathogenicity of pathogens.

Here, I would like to speculate about the origin of the host–parasite relationship in the ancient past. Primitive organisms likely could not find suitable hosts for a parasitic lifestyle. They are thought to have survived by consuming nonliving materials and can be considered to have been nutritionally independent. Later some of them might have become parasites to obtain nutrition from nutritionally independent organisms or hosts.

Parasitism is possible if a host has a surplus of any kind. For example, overpopulation is an important factor in surplus. It is highly likely that parasites were originally nothing more than members of a host population. In their original form, parasites possibly made use of the metabolic activity of other members of the same species. Alternatively, parasitism may have originated as a self-regulatory mechanism against overpopulation. Viruses likely developed as a suicide mechanism to regulate overpopulation.

Later, multicellular life developed and became important hosts for various microbes. In particular, the interior spaces of multicellular life are the best environment for various microorganisms because conditions, including nutrition, temperature, and moisture, remain constant. Parasitic microbes can enjoy this stable environment as long as the host remains alive. On the other hand, saprophytic organisms must frequently endure the more unstable conditions of the natural environment.

The strategy of killing hosts and directly obtaining nutrition from their remains might appear to be efficient, but this strategy is quite unstable. In fact, highly lethal patho-

gens are rare. In other words, as pathogens become more lethal, they become less widely distributed. This fact supports the principle, frequently referred to in this paper, that the environment is indispensable for the survival of living things.

Bacteria are representative parasites of human beings. Some bacteria are highly pathogenic for humans. The hosts of some bacteria are humans and other animals, and the hosts of other bacteria are the soil and the water. The former bacteria are parasites, and the latter bacteria are saprophytes. A saprophyte is indirectly parasitic because its nutrition depends on the metabolic activities of other living things, although its environment is not a living thing.

Tetanus bacilli are considered saprophytes but are frequently found in the digestive tracts of various animals, including human beings. These bacteria are parasitic rather than saprophytic. Furthermore, parasitic pathogens share behaviors with saprophytic pathogens because parasitic pathogens live in isolated sanctuaries in their hosts where they can undergo uncontrolled proliferation. When pathogens are vigorously proliferating they treat their hosts as if they were merely sources of nutrition.

3. Even pathogens cannot survive without their environment

Microbes include various organisms, such as bacteria, fungi, other cellular organisms, and viruses. Bacteria are typical pathogens and cause many infectious diseases. Bacteriology has long been synonymous with microbiology. Medical microbiology has developed as a modern science through the investigation of infectious diseases caused by various bacteria, including diphtheria bacilli, tubercle bacilli, tetanus bacilli, and cholera bacilli.

Few fungi are highly pathogenic, but some fungi become pathogenic in immunocompromised hosts with lowered resistance to pathogens. In medicine, fungi are paradoxical microbes. Many types of fungi produce antibiotics, some of which are used to treat various infectious diseases. Penicillin, for example, the first antibiotic, is produced by the fungus *Penicillium*.

Why some fungi produce antibiotics is an interesting question. One hypothesis is that fungi use antibiotics to try to steal metabolic products produced by nearby bacteria. Used in this way, antibiotics play a similar role to bacterial toxins, such as diphtheria toxin and tetanus toxin. In this case, the fungus is a pathogenic parasite, and the nearby bacteria are hosts.

Furthermore, some fungi parasitize insects and absorb nutrition until the host insect dies. One example is a complex of fungus and caterpillar known as "winter worm, summer grass" in Chinese. These fungi are considered pathogenic because the caterpillars might not be the true host for these fungi. Some fungi live on the skin of humans. They might treat humans as their true host, although they occasionally cause skin inflammation when the resistance of human skin is lowered.

Viruses are noncellular organisms. The morphological unit of viruses is called a virion, which consists of a protein capsule containing nucleic acids, DNA or RNA, as the genome. Viruses are exclusively parasites of cellular organisms. The environment of the virus is the inside of the host cell. Usually, the host–parasite relationship of the virus is specific. For example, a bacteriophage (phage) for which a bacterial cell is the host can never be a parasite of humans or other animals.

Furthermore, phages whose hosts are diphtheria bacilli can never use tetanus bacilli as hosts, and the converse is also true. In other words, only diphtheria bacilli serve as the host for diphtheria phages. The host–parasite relationship of phages is one of main subjects dealt with in this paper.

Prions have recently been considered to be formidable pathogens but are not living things, unlike most other pathogens. Prions are protein molecules. In fact, only abnormal prions cause serious diseases, such as bovine spongiform encephalopathy (mad cow disease) and Creutzfeldt–Jacob disease. Abnormal prions enter nerve cells and convert normal prions into abnormal prions. The accumulation of abnormal prion molecules inside cells causes cellular dysfunction. Even an abnormal prion cannot exist without an organism to support it. From a practical point of view, prions can be regarded as typical pathogens.

4. Infectious diseases occur in the absence of a "true" environment for "pathogens"

Here we will consider the concepts of pathogenicity and commensalism.

In this paper "pathogenicity" is defined as the tendency of a living thing to expand its activity beyond the self-recovery capacity of its environment. On the other hand,

"commensalism" is defined as the tendency of living things to restrict their activities so that a healthy environment is maintained. In other words, every living thing must have a commensal relationship with its true environment and occasionally exhibits pathogenicity against its false environment, or pseudoenvironment.

Disease is a biological condition in which the transport of substances within the body, such as that in the bloodstream, is disturbed. The normal transportation of various substances is required to maintain the health of the body. In infectious diseases, the proliferation of pathogens might disturb the normal transportation currents or cause abnormal currents to develop. The tendency for the functions and processes of the body to be kept in balance is called homeostasis. An example of homeostasis might be the commensal relationship between a parasite and its true environment.

A commensal relationship between parasites and their environment might be stable, simply because the relationship is self-regulating. On the other hand, pathogenicity indicates the breakdown of the "homeostasis" of the system.

For example, the toxin produced by diphtheria bacilli might kill a person, thereby abruptly severing the relationship between the diphtheria bacilli and their host. If humans are the true hosts of diphtheria bacilli, the most dire situation for the bacilli would be the death of a person. The strength of pathogens is usually considered the reason they are harmful to humans. The pathogens are, however, not strong, especially if they have lost their true environments.

Human beings find it hard to accept that pathogens require their environments, because the environments of pathogens are human bodies. Nobody wants their body to serve as an environment for pathogens. Accordingly, many people believe that pathogens can exist without environments. With these beliefs and the invisibility of pathogens, our fear of pathogens is exaggerated. Unfortunately, an exaggerated fear of pathogens is not consistent with rational countermeasures.

If the environment is indispensable, even for pathogens, one might suspect that pathogens have a "true" environment where they could stably and peacefully live. In other words, a parasite might become pathogenic to humans only when the parasite does not recognize humans as their true environment.

For example, fleas of wild rats are the true hosts and environment for plague bacilli. Plague bacilli never exhibit any pathogenicity towards these fleas. As another example, the rabies virus never kills its true host, a South American bat, although this virus is highly virulent for humans. Additionally, neither wolves nor dogs are the true host of the rabies virus, because the virus is lethal to them as well. On the other hand, the bat remains healthy even after being infected with the rabies virus.

5. Infectious diseases classified by host-parasite relationship

The reasons human beings are not the true hosts of pathogens can be classified as follows.

(a) Phages or plasmids as "true" pathogens. In some infectious diseases caused by bacteria, a phage or plasmid residing in the apparent causative bacteria is actually responsible for the disease. For example, the highly lethal growth of diphtheria bacilli at an infection site in a human host is provided with ample nutrition by blood oozing from tissue destroyed by diphtheria toxin. However, the toxin does not originate with the diphtheria bacilli ; instead, a phage designated phage beta is the owner of the toxin gene.

In diphtheria, the true causative agent is the phage, whose true environment is not the human body. In other infectious diseases, plasmids, which are also parasites of bacteria, are the causative agents. For example, the gene for the tetanus toxin resides in the tox plasmid. The human body is also not the true environment of plasmids.

(b) Saprophytic bacteria. Saprophytic bacteria have no fixed host as their environment. Consequently, the human body is not their true environment. Saprophytic bacteria have inherited from their ancestors the common rule about the indispensability of the environment for survival. That is to say, even saprophytic bacteria do not kill other living things simply because they can provide needed nutrition. Very few saprophytic bacteria cause lethal infections. This pathogenic minority of saprophytes must kill quickly because they can obtain nutrition only from the bodies of dead animals, including humans. Virulent saprophytes are likely to be hosts for phages or plasmids carrying genes for toxins or other pathogenic genes.

(c) Zoonosis. A zoonosis is a human infectious disease caused by a microbe whose true host is a non-human animal. Consequently, zoonoses clearly support the hy-

pothesis that infectious diseases in humans occur when humans are not the true host of a parasite or pathogen.

(d) Opportunistic infections. In opportunistic infections, commensal microorganisms exert pathogenicity upon would-be true hosts, while appearing to neglect the principle of maintaining a commensal relationship with their original host. It has clearly been shown that commensal microbes do not change their genetic characteristics even after they cause opportunistic infections. Consequently, the true host likely loses its ability to maintain a stable relationship with commensal microbes. Such a host is a compromised host that allows commensal microorganisms to grow abnormally. Thus, humans are not the true host of all pathogens causing infections in human beings.

Pathogens as Living Things

1. Phages as parasites for bacteria

Phages are not usually considered to be causative agents of human infections. In other words, human beings are neither the true hosts nor the false hosts of phages. Phages are viruses of bacteria, whereas influenza viruses are viruses of animals. More precisely, the environment of viruses, including phages, is the internal spaces of host cells. As a rule, phages inside bacterial cells consist of only DNA or RNA.

Consequently, phage particles, as the morphological unit of the phage, is considered to be a peculiar form of life isolated from its environment. In fact, a phage particle shows no signs of being alive, except when it attaches to the surface of host bacterial cells. Considering the indispensability of the environment for living things, the phage particle is a transient form isolated from its true environment, the host bacteria. Here, let's consider the biological behavior of phages with the assumption that phages are living in specific host bacteria. Consequently, the story should begin when a phage composed of nucleic acids (DNA, in most cases) is present in a host cell. Because RNA phages have a different lifestyle, the following descriptions in this paper will concern only DNA phages. These DNA phages can be divided into two types : virulent phages and temperate phages.

Virulent phages are usually considered to be "typical" phages. Virulent phages continuously proliferate through the destructive consumption of the functions and materials of the host cell. In other words, virulent phages are pathogenic to the host bacteria. In contrast, temperate phages live in host cells without showing any destructive behavior. Because the environment is indispensable for survival, the lives of temperate phages are more rational than those of virulent phages.

The genome of a temperate phage is usually incorporated into the chromosome of the host to become a prophage. The prophage does not reveal its identity during its proliferation as a part of the host chromosome. Furthermore, this type of proliferation seems to be much less efficient than the explosive increase in phage particles seen with virulent phages. Temperate phages, however, can continue to exist as long as the host survives. On the other hand, virulent phages must continuously search for new hosts, i.e., victims, as false environments for destructive proliferation.

Technical terms used for infectious diseases are commonly used to describe the biology of phages. For example, when the DNA of a phage particle has been injected into a new host cell, the phage is said to have "infected" the bacterium. As another example, the term "prophage immunity" is used to describe the phenomenon in which a host bacterium infected by a temperate phage becomes resistant to subsequent infection by another phage of the same species and rejects the injected DNA.

2. The behavior of organisms without a "true" environment

Throughout its life cycle, the virulent phage does not have a stable phase of existence as DNA in a host cell. The ultimate result is an endless chain of production of phage particles and the simultaneous breakdown of the host cell. In other words, a virulent phage always destroys its environment. Consequently, it has no "true" host. The virulent phage seems to be desperately searching for a true host or environment. The virulent phage seems to ignore the common principle of life, the indispensability of the environment for sustainable survival.

A virulent phage is likely to be a mutant of a temperate phage. A virulent phage might be a temperate phage that is no longer able to live peacefully in its true environment, which has now become a vulnerable host. In nature, virulent phages are the minority, partly because finding hosts is difficult. Other than virulent phages, causative agents for highly lethal infectious diseases are rare except during epi-

demic periods.

3. If an organism places a heavy burden on its "true" environment

Under certain conditions temperate phages can also become virulent and produce particles just like those of virulent phages. When the condition of the host bacillus deteriorates, for example, after exposure to ultraviolet irradiation, the phage suddenly begins to proliferate as DNA, and, thus, multiple copies of its DNA are packed into each of numerous protein bags. This process is essentially identical to that of virulent phages. When phage particles are being produced, the host bacilli might be destroyed.

Just as a virulent phage does, the temperate phage in the form of a particle tries to make contact with a new, adjacent host and inject its DNA into it. Unlike that of virulent phages, however, the newly injected DNA of temperate phages might become integrated with the chromosomes of some hosts. Simultaneously, the genetic characteristics of the host bacillus might change through the new genes provided by the phage.

When a temperate phage, designated phage beta, is incorporated into a host — the diphtheria bacillus, for example — the host begins to produce the toxin causing diphtheria, a life-threatening infection. If the environment is indispensable for the survival of organisms, why does a bacillus containing phage DNA produce a destructive toxin to destroy its own environment?

4. Diphtheria bacilli intrinsically produce no toxin

A diphtheria bacillus containing no phage beta produces no toxin and causes no severe diseases, such as diphtheria. The bacillus lives in the throats of some persons as a commensal microbe. Furthermore, no phage beta lacking the toxin gene has ever been found. Therefore, a reasonable conclusion is that the diphtheria bacillus as a commensal microbe produces no toxin because doing so would lead to the destruction of its true environment. Consequently, toxin production might be required for phages but be unnecessary or even harmful for the diphtheria bacillus.

That the diphtheria bacillus does not "want" to cause diphtheria might appear paradoxical and be difficult to understand but is consistent with the principle of the indispensability of the environment for survival.

5. Why does phage beta allow the host bacillus to produce diphtheria toxin?

Phage beta does not destroy the host diphtheria bacillus if the bacillus is healthy. In other words, for its continuing survival, phage beta must "expect" its host to be healthy. A problem, however, is that the presence of phage beta is inconsistent with the health of the host because its competition for survival with phage-free rivals might jeopardize the phage's own survival. The phage must compensate for its burden on the host due to the consumption of materials and energy for the phage DNA. As the source of the facilitated supply of nutrition for the host bacillus, the human body is the single target for the phage. If sufficient nutrition can be obtained from the human body, a diphtheria bacillus can overcome the burden of hosting phage beta.

Diphtheria toxin destroys the mucous membrane at the infection site. The destruction of the mucous membrane causes capillary rupture and bleeding. The extensive growth of diphtheria bacilli supported by the nutrition provided by the blood results in greater production of toxin.

Some of the toxin molecules might enter the bloodstream through the injured vessels and be distributed throughout the body. The toxin kills mainly the muscle cells of the heart, and the infected persons frequently "die of diphtheria" because of heart failure.

The death of the infected host means that the diphtheria bacilli lose their true environment. The bacilli must then leave a dying host to find a new, healthy host, just as virulent phages do. Toxin production by the diphtheria bacillus might violate the principle of the indispensability of environment, but it is completely reasonable from the point of view of phage beta because the human body is not the true environment of phage beta. Therefore, the real pathogen of diphtheria is not the diphtheria bacillus but phage beta.

6. Diphtheria toxin is like the intelligence of human beings

According to the logic of phage beta, the human body is not an indispensable environment but is nothing more than a source of nutrition for the diphtheria bacillus, although the human body is undoubtedly an indispensable environment for the survival of diphtheria bacilli. This fact might suggest that the natural environment is not the true environment of human beings, although the natural environment is, in fact, indispensable for the human body. According to the

logic of the human mind, the natural environment is nothing more than a source of materials to allow the human body to live comfortably ; however, nature is, in fact, the environment of the human body.

In general terms, "human" usually does not refer to the human body but instead to the human mind. In a similar way, phage beta might correspond to the human mind, and diphtheria toxin might correspond to human intelligence. Furthermore, the high intelligence of human beings is not a product based on the demands of the human body but is instead based on the demands of the human mind. An enlarged brain consumes large amounts of energy. Therefore, a body with a larger brain cannot stay healthy with the amount of energy that can support bodies with smaller brains.

An enlarged brain might lead to higher intelligence so that the nutritional needs of the body can be met, just as phage beta provides the toxin gene to the diphtheria bacillus. Conversely, the human body might not be able to obtain enough food without the higher intelligence of a larger brain. As a result, the brain, which was once just a part of the body, has become the master of the human body.

The diphtheria bacillus might obtain a new way of life as a virulent pathogen through the activity of the diphtheria toxin but might discard the principle that the true environment is indispensable. In other words, phage beta might become a "tyrannical" parasite when the diphtheria bacillus begins to depend upon the powerful activity of the diphtheria toxin.

7. Useful genes and useless genes

As mentioned earlier, phage genes produce phage particles. They do not contribute at all to the survival of the host bacillus. In other words, the phage genes are selfish and are useless to the host. Consequently, the phage genes must compensate in some way for their selfishness and the burden they place on the host through their parasitism. The toxin gene can be especially useful to phage beta for solving this problem but cannot be useful unless phage beta has a reason to maintain a stable existence in the host bacteria.

Paradoxically, a gene cannot survive and be useful unless a selfish or useless gene has a "desire for survival." Phage beta has lost its selfishness or uselessness by donating the toxin gene to the host bacillus, although it retains its selfishness in an emergency to produce particles and destroy the host bacillus. On the other hand, the toxin gene can justify its existence by becoming a part of phage beta. At any rate, both selfish genes and useful genes might be able to stably co-exist by combining with each other.

8. Role of useless genes

Richard Dawkins has written that every gene is selfish. According to his theory, every gene has genetically useful information simply because of its survival or stable existence. In other words, a gene that does not provide genetic information useful to other organisms cannot survive. Ironically, according to this logic only useful genes can survive.

As I understand them, only useless genes are selfish. The useless gene wants only to exist as a nucleic acid. In other words, it does not want to exist as a useful part of other living things. Paradoxically, such a useless gene must disguise itself as a useful gene because an apparently useless gene has no chance to be incorporated into any living thing. Although a gene itself is not alive, it does, however, share with living things the principle of continuous existence. For its environment, a gene must depend on the stable existence of a living thing.

In other words, a useless gene must pretend to be useful, or at least harmless, to become a part of an environment or host. Consequently, the useless gene might lose its selfish identity when it becomes part of a host. The best example is a temperate phage with a useful gene. On the other hand, a virulent phage is typically selfish. It does not have to pretend to be useful to the host bacillus.

The behavior of a virulent phage should be considered abnormal rather than selfish simply because it cannot live in its true host or environment. A temperate phage, however, cannot recognize that its environment or host is also a living thing that depends upon another environment, its true environment, the human body. Phage beta could be useful to the diphtheria bacillus through its toxin but simultaneously threatens the stable existence of the host bacillus by producing abnormal conditions within the human body.

Phage beta cannot use every gene to produce a phage particle in order to continue to exist stably in the host bacillus. When these genes are shown to be useful, the fundamental relationship between the phage and the host bacillus

is destroyed. In this sense, the usefulness of the phage genes is ambiguous.

Similarly the toxin gene is useful to phage beta but not to the diphtheria bacillus because the toxin might deprive the diphtheria bacillus of a stable environment, although the toxin provides short-lived prosperity with an ample supply of nutrition from the human body. In a way, the toxin gene might also be selfish. It might, along with phage beta, pretend to be useful to the diphtheria bacillus.

As an analogy, phage beta might use the toxin gene and the abundant source of nutrition it provides to lure the diphtheria bacillus. The diphtheria bacillus might give in to the temptation from the phage and give up its right to expect modest but stable support from the human body. It could be said that the diphtheria bacillus has evolved into a pathogen by donating the toxin gene.

In a similar way, the powerful effects of intelligence provided by an enlarged brain might lure the human body into neglecting its harmonious existence with nature.

The higher intelligence of the human brain provides the human body with a rich environment modified from the natural world. In other words, the human brain had to provide the human body with a new environment or world in the brain itself because the human brain had to overcome its uselessness in the human body, which lives in nature like the bodies of other animals.

9. Infectious diseases as a result of encounters between selfish living things

In the host-parasite relationship, infectious diseases occur when a stable state has not been established between a host and a parasite. Parasites can be classified as intrinsic or extrinsic. Commensal microbes are examples of intrinsic parasites. Usually, commensal microbes live as normal inhabitants of a host, although they might have originally come from another person, most often the mother just after birth.

A temperate phage is an intrinsic parasite of the host bacillus. In a similar way, the human brain can be thought of as an intrinsic parasite of the human body. The human brain behaves as if it were independent from the body, just as a phage might become a particle if it were independent from the host bacteria.

Returning to the present subject, even pathogenic microbes have no desire to attack or destroy their hosts. Consequently, an infectious disease should not be likened to a war or a life-and-death struggle.

On the other hand, an infectious disease is like a proxy war. The true and formidable enemy of the pathogen is not the human body but the brain or intelligence.

In this war, the human body can be seen as a battlefield with rather peaceful inhabitants. The human brain, with its high intelligence, should be a military adviser with a mission to protect the human body. In this analogy, the human brain considers the human body to be its vital colony and considers pathogens to be an invading enemy or rival that intends to threaten its lifeline. This might be the best explanation for why human beings aggressively hate pathogenic microbes and try to eradicate them.

From the point of view of the diphtheria bacillus, phage beta with its toxin gene is like a military adviser who persuades a peaceful diphtheria bacillus to use a horrible weapon. In this war the human brain might be at a great disadvantage because the human body is its true environment, but for the phage beta the human body is nothing more than a source of nutrition. Phage beta might survive, even if the patient dies, as long as the host bacillus can move to a new host ; in contrast, the human brain dies when the body dies.

10. The essential dilemma between proliferation and existence

In general, the unlimited proliferation of a living thing would destroy its environment, which has a limited capacity to support life. As mentioned earlier, every parasite or living thing has an established system for sustainability with its true environment. As a rule, a pathogen might excessively proliferate in its host environment if a suitable system for a sustainable relationship is absent.

Some pathogens have an alternative means of survival to compensate for the lack of a system to maintain the condition of its host. Parasites can survive if they can continue finding new hosts. To increase their chances of finding new hosts, parasites must vigorously proliferate. This proliferation is why many infectious diseases are lethal. Consequently, pathogens, as causative agents for communicable diseases, might violate the universal law regarding the indispensability of the environment, although such pathogens are supposed to have true hosts elsewhere.

There is another reason why unnecessarily vigorous

proliferation and widespread distribution of hosts are required for outbreaks of communicable diseases. Unlimited proliferation might be possible only if the number of hosts is also unlimited. However, hosts and environments are unlimited only in artificial situations, such as laboratory bacterial cultures and livestock feedlots. Outbreaks of communicable diseases end when causative agents cannot find new hosts as bases for proliferation.

Pathogens as causative agents for communicable diseases must use unstable ways to exist if they cannot find their true hosts. Nevertheless, pathogens are considered hardy and powerful because they can survive even after their hosts die. Such pathogens are, however, paradoxically weak organisms because they cannot find the true hosts in which their fellow pathogens are living without expressing pathogenicity.

Pathogens might even control their proliferation to establish a stable relationship with their host. However, it is widely believed that living things with a greater proliferative capacity should be successful or prosperous. This belief might be supported in part by the agricultural point of view, in which abundant proliferation is seen as prosperity. If the supply of nutrients is unlimited, proliferation might indicate the superiority of an organism. In the real world, however, the resources for supporting a living thing are always limited. Similarly, even microbes, including pathogens, have a limited life span determined by the supporting capacity of their environments or hosts.

Considering the predetermined supporting capacity or life span of an environment, we can conclude that any living thing, even a pathogen, must limit its consumption of energy and of materials from its environment or host to ensure longer survival. Consequently, explosive proliferation will lead to an ephemeral existence. Therefore, a reasonable conclusion is that the diphtheria bacillus does not produce diphtheria toxin by itself.

Interestingly, phage beta is anticipated to undergo a blindly explosive proliferation. Phage beta should regard its toxin as an effective tool that provides the host bacillus with a survival advantage over commensal rivals, including phage-free diphtheria bacilli. Phage beta cannot "see" that the uncontrolled growth of a host bacillus and the subsequent death of the patient should result in an unstable life for its host and for itself.

11. Multicellular organisms are possibly products of useless genes

I would like to suggest the hypothesis that multicellular organisms are products of useless genes.

The survival of useless genes, such as those of phages, might produce undesirable conditions for the host, mainly by violating the basic law about the indispensability of the environment. I speculate that a useless gene might have played a vital role when the ancestors of multicellular organisms developed from their unicellular predecessors. The basic rules for existence might differ greatly between unicellular and multicellular organisms. For example, unicellular organisms might hate overcrowding and prefer to express all their genes.

However, in a multicellular organism, each cell or former organism might be forced to endure extreme crowding and limited expression of its genes. A useless gene might be most appropriate for the compromises that must be made among cells to establish a multicellular system, in part because such a useless gene has no desire to express itself other than to ensure its existence. In other words, a useless gene is naturally content with its role in a multicellular organism.

The useless gene might develop a system to guarantee that genes in sex cells are preserved in exchange for the limited expression of genes in other cells that agree to become a member of a multicellular organism. The useless gene might have persuaded each cell to choose a longer and more stable existence as part of a multicellular organism instead of accelerated proliferation as a unicellular organism. This shift in strategy might resolve the dilemma between proliferation and continued survival.

Considering that the limited expression of genes means that cells play different roles in a multicellular organization, the useless gene might coordinate the genetic consolidation necessary to create a multicellular organism. Becoming a coordinator might be only one way that useless genes compromise and become useful. In other words, even the useless gene has to become useful to stably survive.

Paradoxically, the human mind is a prime example of selfishness or uselessness. As previously described, the human mind would like to have a stable existence by providing intelligence to the human body and persuading it that the mind is useful. The intelligence provided by the hu-

man mind is not requested by the body but is a tool used by the mind to control the body. I hope that readers of this paper might see a great similarity between phage beta and the human mind in the relationship to their environments : the diphtheria bacillus for phage beta, and the human body for the human mind.

12. Plasmids allow the tetanus bacilli to produce a strong toxin

The plasmid is another parasite whose relationship with its environment is similar to that of a temperate phage with its host bacillus. The selfishness of the plasmid is less obvious than that of the temperate phage. Usually, several copies of a plasmid reside in a host bacillus. The plasmid never becomes particles, as does the temperate phage, even when the host bacillus is going to die. Consequently, the plasmid is more dependent upon its host bacillus as its environment than are temperate phages, although some species of plasmid can move to a new host through a bridge formed between two host microorganisms.

Several pathogenic bacteria produce their own disease-causing toxins using genes provided by plasmids. The reason the plasmid contains a toxin gene is the same as for the temperate phage. Tetanus toxin is highly lethal to various animals, including humans. The lethality of the tetanus toxin is consistent with the saprophytic lifestyle of the tetanus bacillus, which can metabolize only the dead bodies or body parts of animals.

The botulinus bacillus also produces a highly lethal toxin similar to tetanus toxin. In fact, both toxins share the same ancestor gene. A temperate phage possesses the gene for botulinus toxin. These facts suggest a common rule controlling both the plasmid and the temperate phage. In the case of botulism, the toxin gene might give the host bacillus an advantage in obtaining nutrition from an intoxicated victim.

Some plasmids confer upon their host bacilli resistance to various antibiotics. This phenomenon can also be explained as a strategy of the plasmid to ensure the survival of its host bacillus. Ironically, human beings give plasmids the chance to confer drug resistance upon their host bacilli.

BIOLOGICAL BEHAVIOR OF VARIOUS PATHOGENS

1. Vaccination is performed with the slowness of the immune system in mind

Tetanus can be effectively prevented by appropriate vaccination with the tetanus toxoid. The toxoid is a toxin molecule whose toxic activity has been eliminated chemically. The vaccination might have a stronger effect on the life of plasmids than on the life of the host bacillus, although human beings are a minor prey species for tetanus bacilli. When vaccination is effective, the strategy of the plasmid becomes useless. Incidentally, the immunity against tetanus gained through vaccination can be considered "artificial," because immunity is never established during the usual course of tetanus infection. The amount of toxin large enough to kill a person is too small to stimulate the immune system.

The extreme toxicity of tetanus toxin and of botulism toxin suggests that pathogenic saprophytes do not intend to allow their victims to survive their infections. For these saprophytes, death is a successful result, unlike for parasitic pathogens. These explanations are reasonable if plasmids are not recognized as real pathogens.

2. The identity of plasmids is clonal

There is an interesting phenomenon in the behavior of the plasmid in tetanus. As mentioned above, tetanus toxin is highly lethal. Ironically, a tetanus bacillus that produces toxin cannot derive any benefit from it because the bacillus is destroyed when it releases the toxin. A minority of tetanus bacilli in a population produce toxin ; the majority of bacilli, which do not produce toxin, reap the nutritional benefits of the toxin's effects and proliferate explosively.

Identical plasmid molecules reside in each surviving bacillus, and many plasmid clones survive thanks to the deaths of a small number of toxin-producing bacilli. Consequently, the preservation of plasmids is established on a clonal basis rather than on a molecular basis. In this sense, the preservation of a plasmid is in contrast to the preservation of the individuality of human beings. The continued existence of a person's identity comes at the expense of the cells of the body, which are continuously born and die.

3. Even saprophytes do not kill living nutrition sources

Most saprophytes are not pathogenic. However, tetanus is an infectious disease caused by saprophytic pathogens. The rarity of saprophytic pathogens suggests that even saprophytes cannot ignore the principle that the environment is indispensable for living things. Saprophytes are completely dependent upon other living things. Consequently, even the tetanus bacillus cannot kill animals by itself. The plasmid is the true agent of tetanus, just as phage beta is the true agent of diphtheria.

4. The human being is not the "true" host for tubercle bacilli?

Tuberculosis is a good example of an infectious disease in human beings. Humans are widely believed to be the true host of the tubercle bacillus. In fact, tubercle bacilli can establish their infection cycle only among human beings, but the pathogen very often kills people through the progressive destruction of their bodies. On the other hand, the tubercle bacillus confers immunity to many persons through natural infection.

Paradoxically, persons who have accepted a small population of tubercle bacilli living in their lungs might acquire immunity to them. Only infection by living bacilli can efficiently activate the immune system of the host. This phenomenon is called "infection immunity."

Infection immunity is a paradoxical concept because immunity is usually defined as a biological state to prevent infection by pathogens. In the case of tuberculosis, a stable immunity might be established after a long-lasting infection by tubercle bacilli. The immunity against tubercle bacilli is indicated by a positive reaction on the tuberculin skin test. Symptoms, such as induration and skin reddening, reflect the increased function of activated white blood cells called macrophages. Macrophages functioning at the nonactivated level might fail to stop infection by tubercle bacilli.

The increased function of activated macrophages might be a double-edged sword. Activated macrophages can efficiently ingest and kill tubercle bacilli. On the other hand, the massive release of digestive enzymes from macrophages injured or killed during fighting with tubercle bacilli destroys the structure of the lung. Finally, the destruction might reach air ducts and allow a tunnel to be formed between them and the infection site. Thus, the tubercle bacilli find a way to complete their infection cycle.

At the same time, the infection site becomes better able to support the proliferation of tubercle bacilli. The infection site is a cavity with abundant nutrition coming through its wall and abundant air coming through air ducts. Furthermore, even activated macrophages cannot enter the cavity. Persons with cavities in their lungs allow tubercle bacilli to vigorously proliferate by continuously providing nutrients, occasionally until they become nutritionally exhausted and die.

5. Why do tubercle bacilli provide immunity to most people?

Even patients with pulmonary tuberculosis have immunity against tubercle bacilli. Tubercle bacilli cannot establish a stable proliferation system in an infected person who does not have normal immune function. Neonates are immunologically immature, especially against tubercle bacilli. They cannot properly develop infection immunity against tubercle bacilli and frequently die shortly after tubercle bacilli begin to grow at an explosive rate throughout their bodies. Usually, no cavities are found in their lungs. Immunologically immature neonates are not true hosts for tubercle bacilli because they cannot develop immunity against tubercle bacilli and do not allow them to proliferate and to infect a new host. Paradoxically, only hosts having mature immune function can form a cavity after developing infection immunity in response to tubercle bacilli.

Tubercle bacilli have no host on which their stable existence depends. In other words, they are not inherently parasitic but rather saprophytic in nature. Tubercle bacilli make dual use of the immunological reactivity of hosts to provide immunity to most persons and to create cavities in infected persons as reliable sites for their growth. Tubercle bacilli require two types of host – healthy persons and infected persons – to produce their progeny. The bacilli seem to be commensal rather than pathogenic to healthy persons with infection immunity. They coexist peacefully with living hosts. When these healthy hosts die of other causes, the tubercle bacilli have no exit route and cannot spread to other persons. Consequently, persons with tuberculosis are absolutely indispensable for the continuous existence of tubercle bacilli.

Why are some animal diseases occasionally life-threatening to human beings?

As frequently noted in this paper, every microorganism has its own true environment. However, conditions for

establishing the true relationship between microorganisms and their environments might be complex. However, a true relationship is extraordinarily stable and is supported by numerous factors.

In this sense, we can easily understand why some animal diseases, called zoonoses, are dangerous to human beings. Agents causing zoonoses have true hosts other than human beings and lack a mechanism to establish a stable coexistence with the human body. In other words, they have no true relationship with humans. On the other hand, most microorganisms parasitizing nonhuman animals are generally harmless to humans because they also cannot establish a stable existence in the human body.

6. Human plague is a fruitless expansion for plague bacilli

Bubonic plague has been one of the most devastating communicable diseases in human history. People during the Middle Ages did not understand why such a disease periodically came to kill so many. Seeking a religious answer was as reasonable a course as any. Dirty and overcrowded cities were ideal incubators for frequent outbreaks of plague. Life in cities is generally more artificial than life in rural areas.

In a sense, "artificial" means "not true." In fact, the true hosts of the plague bacillus, the causative agent for plague, are fleas parasitizing wild rats. The fleas are never killed by the plague bacillus, but wild rats are vulnerable to infection. When too many wild rats are killed, the fleas cannot find a suitable source for blood. Hungry fleas then obtain blood from people, who are not their usual source of blood. Plague bacilli might then grow throughout the human body. Plague bacilli growing in the lungs are emitted with sputum and allow the disease to spread through the air, as influenza does. Some respiratory infections are highly communicable because animals must breathe to survive. This aerosol, communicable type of plague is more accurately called pneumonic plague.

Fleas play no role in the spread of pneumonic plague among humans. In other words, plague bacilli have become completely separated from their true host in pneumonic plague, although they could proliferate explosively during epidemics among humans. Plague bacilli might completely disappear from a human population immediately after the end of each epidemic because they cannot find their true host. Plague bacilli might not be able to return to fleas of wild rats, even though they have proliferated wildly in human beings.

Humans frequently die of zoonoses because there is no mechanism to maintain the stable coexistence of microorganisms and humans. Such mechanisms have been meticulously developed during the long history of the host–parasite relationship. In other words, the divergence of hosts should reflect the divergence of parasites, and vice versa. For example, the herpes B virus is highly lethal to humans but is commensal in monkeys, just as the herpes simplex virus is commensal in humans.

Our ancestors diverged from earlier apes and changed their biological behavior to avoid lethal infections. Thus, the change in the host–parasite relationship might be an important cause of biological development. Most zoonoses are caused by careless contact with animals carrying causative microorganisms that are commensal in them.

7. Biological behavior of influenza viruses

The true hosts of influenza viruses are wild birds. Influenza viruses are harmless for wild birds and maintain peaceful infection cycles through the birds' digestive tract. Influenza viruses can sometimes find an infection route to humans via pigs when they have acquired a mutation that expands their choice of host. Pigs are domesticated animals living close to humans. Domesticated animals usually live in far greater concentrations than do wild animals. Pigs play an essential role in influenza epidemics among humans, just as fleas do in plague.

Influenza viruses can acquire mutations to become highly virulent, even to birds. Such mutant viruses grow uncontrollably in birds and often kill their hosts. In nature, these virulent mutants rarely survive because they cannot maintain a stable existence owing to their high lethality and scarcity in bird populations.

When virulent mutant viruses infect a chicken farm, many chickens are likely to die. The mutant is equally lethal to humans, probably because the mutants lack a mechanism for commensal behavior. If such a mutation were acquired by an ordinary influenza virus, a worldwide epidemic, as deadly as the plagues of medieval Europe, might occur.

8. Host crowding is required for epidemics of communicable diseases

Rural life is generally uncrowded but slow. In contrast, urban life is efficient and concentrated. A high density of hosts is the most favorable condition for epidemics of communicable diseases. Of animals with sizable bodies, humans live in the most crowded conditions.

9. Human beings are not the "true" host to pathogens for opportunistic infection?

Opportunistic infections are caused by commensal microorganisms. In other words, parasites in opportunistic infections seem to exhibit pathogenicity to their true hosts. The principle this paper has often referred to, the indispensability of a host for the stable survival of a parasite, seems to be ignored in opportunistic infections. Causative agents for opportunistic infections are genetically unchanged, even when they become pathogenic.

Opportunistic infections might suggest that the host–parasite relationship is established through the conditions of both the host and the parasite. In opportunistic infections, the host lacks the requirements to be a true host to commensal parasites. Patients with an opportunistic infection are called compromised hosts. They give the causative agents unnecessarily large amounts of nutrients for the commensal way of life owing to a loss of homeostasis.

Homeostasis is the maintenance of stable conditions for living things, including human beings, so that they can remain healthy. In general, living things maintain constant internal conditions, even when the condition of their environment has changed in a dangerous way. Homeostasis is established with blood and other fluids of the body to obtain nutrition from the environment and excrete waste to the environment.

In other words, the environment is indispensable for living things to achieve homeostasis. Living things sometimes lose homeostasis because of accidents and diseases, including infections. Diseases can be defined as conditions "out of homeostasis." Opportunistic infections are secondary disorders that follow a loss of homeostasis. A host that has lost homeostasis cannot control commensal microorganisms from becoming noncommensal.

In general, opportunistic infections might be resolved as soon as the host recovers homeostasis, despite the infection not having been treated. Ironically, some treatments, such as catheterization and chemotherapy, for malignant tumors might cause opportunistic infections because of the host's loss of homeostasis.

Paradoxically, catheterization frequently disrupts normal blood flow at the site of catheterization. Chemotherapy for malignancies might suppress immunologically competent cells. The immune system is important for homeostasis, because the actions of the immune system are needed to eliminate foreign bodies with immunological markers.

10. Homeostasis is an essential mechanism for resisting infectious diseases

"Foreign body" is an important term for understanding homeostasis. In the broadest sense, a foreign body is a substance that disturbs homeostatic mechanisms. Pathogenic microbes are examples of foreign bodies. Infections usually disturb homeostasis. On the other hand, disturbances of homeostasis allow opportunistic infections. In other words, commensal parasites become foreign bodies and promote the disturbance of homeostasis.

Heterotopic infection is a kind of opportunistic infection. In a compromised host, commensal parasites might proliferate abnormally in a part of the body that is not their true environment. The parasites cannot find an exit from the body, although they have vigorously proliferated at the infection site. In other words, they cannot establish an infection cycle.

Poliovirus is relatively harmless for most people. It usually completes its infection cycle through the digestive tract without causing severe symptoms. In rare cases, the virus successfully infects nerve cells controlling the muscles of the extremities, usually the lower limbs. The destruction of the nerve cells by the proliferating poliovirus might result in paralysis of the limbs. Although the polioviruses have vigorously proliferated, they cannot find an exit to infect a new host. The proliferation of poliovirus in nerve cells is biologically futile simply because poliovirus cannot find an exit to reach a new host.

11. Adults are more vulnerable than newborns to hepatitis B infection

In some infectious diseases, a specific type of person is the true host for a parasite. A newborn might become a carrier of the hepatitis B virus if the virus is passed from

the mother through the blood at birth. Carriers of the hepatitis B virus cannot eradicate it from their bodies because they do not recognize the virus as foreign. Persons with a normal immune system would eliminate liver cells containing the hepatitis virus to eradicate the virus. In other words, virus-infected liver cells become foreign bodies in these persons. If many liver cells in a previously healthy adult are infected by the hepatitis B virus, the resulting massive cell death can be life-threatening. In contrast, newborns might not eradicate virus-containing liver cells because their immune systems are immature. Paradoxically, severe hepatitis might not develop in newborns even after a massive infection because they cannot eradicate virus-infected hepatic cells.

The true hosts of the hepatitis B virus might be newborns because only newborns allow the stable existence of hepatitis B virus through maternal transmission. Mothers carrying the hepatitis B virus conceive and bear children, who themselves become carriers. The hepatitis B virus might "hope" the child is a girl because she is the best candidate as a true host.

12. Are infants "true" hosts in varicella-zoster infection?

The varicella-zoster virus causes entirely different types of infection depending on the age of the host. When the host is an infant, primary infection by this virus occurs in the form of varicella. Varicella is usually not lethal, but the virus is not eradicated and remains in the host. Later, latent varicella virus will be activated to cause zoster, another form of the infectious disease caused by this virus, when the host becomes compromised. The skin lesion of zoster might be an efficient way for the virus to infect infants.

Consequently, an infection cycle is formed between children and older persons. In this sense, varicella/zoster is a vertical infection that sometimes skips a generation. It is not a typical vertical infection from mother to infant but instead targets different generations.

13. AIDS as a sexually transmitted disease

The causative agent for acquired immunodeficiency syndrome (AIDS) is the human immunodeficiency virus (HIV), whose true host is believed to be an African monkey. Consequently, HIV might reasonably be expected to cause an infectious disease in humans. AIDS is usually a sexually transmitted disease. In other words, the sexual activity of humans gives HIV a chance to cause infections among humans.

Sexually transmitted diseases are also called venereal diseases, after Venus, the Roman goddess of love. Sexual activity is required for reproduction in many species. Sexual activity is usually strictly limited to a particular time of year due to the hormonal regulation, unlike the drive to preserve the individual. Only humans are free from the seasonal restriction in sexual activity.

The sexual behavior of humans provides HIV with a new route of infection. Of course, iatrogenic infections from blood or blood products are equally specific for humans. The highly artificial conditions provided by the high intelligence of humans also provide the virus with a new route of infection.

14. Desire is a stubborn parasite in the mental environment of humans

In other words, HIV makes use of the human mind, which is a virtual environment supported by the highly developed human brain. Causative agents for sexually transmitted diseases might be like puppets manipulated by the human mind, and the real agent might be sexual desire, whose environment is the human brain. In some cases the desire might become pathogenic when the mental environment is compromised, just as commensal microorganisms can become pathogenic in compromised hosts.

A Chinese proverb states : "It is rather easy to eradicate bandits, but it is not so easy to overcome the inner bandit, greed derived from desires."

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