Microbes or man, who will win ? (extended summary)

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Introduction

Once the cause of infectious diseases had been uncovered, mainly thanks to the work of Robert Koch, Louis Pasteur and their followers at the end of the nineteenth and the beginning of the twentieth century, a multivalent strategy was implemented to prevent and control microbial infections due to bacteria, viruses or parasites. Thanks to hygiene, the control of insect vectors, vaccination and the wide use of antibiotics, the most dangerous and widespread infectious diseases could be more or less controlled, at least in developed countries. Hence the impression, in the 1970s, that the fight against infectious diseases had been won.

This was a major mistake. Beginning at the end of the 1970s, several new infectious diseases have emerged, some of them, like AIDS, taking hundreds of thousands or even millions of lives every year. In this presentation, on a few examples, we analyze the causes of this emergence and then review the new actions that are or could be taken to control infectious diseases.

How and why do new infectious diseases emerge ?

The three events of 1976

Retrospectively, the year 1976 constituted a turning point. It was the year where mankind was just about to win its most spectacular victory against infectious diseases, the eradication of smallpox. During that same year, three infectious diseases, unknown before, caused small epidemics : legionellosis which owes its name to that of its first known victims, members of the *American Legion* who had gathered for a meeting in Philadelphia ; Lyme disease named after the small village where it was first identified, and Ebola fever named after a small river close to a village in Zaïre where a first epidemic was identified.

In these three instances, the microbes that caused the disease were not new, even though they had not been identified previously. They pre-existed, each in its own habitat. *Legionella pneumophila* is an environmental bacterium that usually lives in rivers, lakes or ponds. *Borrelia burgdorferi*, the cause of Lyme disease, is a bacterium that parasites several species of mammals, especially deer and that is transmitted by ticks. As for Ebola virus, its reservoir seems to be a species of bats. These microbes started to cause epidemics because of the changes in the mode of life of man. It is the development of air conditioning that provided *Legionella* with a new habitat – the residual water in air conditioning towers – from which it could reach human pulmonary cells. It is the change in the living habits of people in New England that, by, bringing human and deer populations close to one another created the conditions for a spread of Lyme disease. Finally, it is the installation of insufficiently equipped small hospitals with inadequate hygiene practices in the wilds of Africa that caused the epidemics of Ebola fever ; indeed, any patient infected with this virus and looking for a cure in such a hospital readily contaminated the doctors, the nurses and the other patients. Since 1976, these three diseases continue to be present wherever the conditions are fit for them to spread.

As these three examples show, it is often man himself who causes the emergence of new infectious diseases. Many other examples could be given, but let us stop for a few minutes on the symbolic case of AIDS.

AIDS

Once again, the most likely scenario for the emergence of AIDS in the early 1980's illustrates how changes in the lifestyle of human societies provoked the emergence of this disease that has become the most deadly of all infectious diseases, with about 3 million deaths each year.

There is presently no doubt that the AIDS virus came from apes, since HIV1 is indistinguishable from a chimpanzee virus. Since inhabitants of the villages of central Africa often go to the wilds in order to kill and eat apes, the chance is great that they can be contaminated while

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carving the meat from these animals, which can be asymptomatic carriers of the virus. Then there is evidence that once the virus has been introduced in such a village it fails to spread because of the local social traditions (no prostitution, no intravenous drug use). Indeed, it was found that in a village where 1 % of the population had been seropositive in 1976, this proportion was identical 9 years later. However, probably because of the general rural depopulation, a few infected persons may have left their villages to go and live in Kinshasa where prostitution and intravenous drug use were rampant. Thus, the virus was given all opportunities to diffuse within the town and then, because of the development of tourism and international travel, from there to the rest of the world. Finally, in the western world, especially in the USA, the sexual habits that had developed in the gay community, involving extreme cases of promiscuity, gave a further boost to the epidemic.

Numerous other examples could be presented of the role of mankind in the emergence of new diseases**.** However, an additional factor is also often at work in the emergence or re-emergence of infectious diseases. It is the remarkable adaptation capacities of microbes.

Resistance to anti-infectious agents

A first and well known example of adaptation is the acquisition by microbes of the ability to resist the action of anti-infectious agents such as antibiotics.

An antibiotic is a molecule that blocks a chemical reaction essential for the growth and multiplication of a bacterium. Usually, it acts by inhibiting an enzyme catalyzing such reaction. Many resistance mechanisms have been uncovered, all preventing the interaction of the antibiotic with its target. For example :

- Alteration of membrane permeability
- Modification of the target enzyme
- Short circuit of the target enzyme
- Production of an enzyme destroying or modifying the antibiotic
- Efflux pumps

These resistance mechanisms result either from mutations or from the acquisition of genes from other bacterial species.

Because antibiotics have been used extensively, and sometimes improperly, in human medicine as well as by veterinarians, antibiotic resistance is now observed in an increasingly worrying proportion of pathogenic bacteria. As a consequence, certain infectious diseases that were easily controlled a few years ago have become very difficult, if not impossible to cure. This is the case, among others, for tuberculosis, the second most deadly infectious disease after AIDS, with about 9 million cases and 2 million deaths each year. According to the most recent statistics, about 5 % of the new cases are due to bacteria that resist most of the antibiotics used in the treatment of the disease.

Flu : adaptation to the immune defence and crossing of the species barrier

The re-emergence of an infectious disease can result from another type of adaptation than resistance to a drug. It may result, for instance, from a resistance to the immune defence of the infected hosts, or to the ability to cross a species barrier. The influenza virus provides examples of these two possibilities.

At its surface, this virus bears two molecules, called haemagglutinin and neuraminidase (H and N), that allow it to bind to host cells. When a young individual in good health is infected by this virus, he is sick, but he fights back by developing an immune response, learning, in particular, to produce antibodies that bind the H and N molecules and therefore prevent the virus from binding to host cells. The patient then recovers and, if he is re-infected by the same virus, he immediately produces the antibodies which stop the infection. A similar protection can be obtained through vaccination, the vaccine consisting in killed virus. However, this protection is only temporary. Indeed, the virus evolves permanently. Mutations occur that slightly alter the H and N molecules in such way that the virus escapes detection by the antibodies present in people that were either previously infected or vaccinated. Viruses bearing theses mutations obviously benefit from a selective advantage. The virus thus shows its ability to overcome immune defences. Hence the necessity to be re-vaccinated every year, the vaccine being adapted to the changes in the virus.

In addition to this slow evolution of the virus, sudden changes occur from time to time, with dreadful consequences. Everyone remembers the awful epidemic of the “Spanish flu”, in 1918-1919, that caused between 20 and 50 million deaths. About half of the world population was infected and half of them were sick. Two other epidemics of lower amplitude occurred in 1957 and 1968. These recurring epidemics, qualified of pandemics because they concern the whole world, are due either to infections by avian influenza virus or to hybrids between such viruses and human viruses. These viruses bear H and N molecules never seen before by human beings, who are therefore totally devoid of protecting antibodies. Hence the very high number of deaths resulting from infections by such influenza viruses that have crossed the species barrier.

A major concern since 2003 has been that the deadly H5N1 avian virus, that proved highly pathogenic for birds as well as for the some 400 individuals that were infected through contacts with infected birds, adapt to human beings in such a way that it becomes contagious. More recently, another influenza virus, A (H1N1), a hybrid between human, porcine and avian viruses, is responsible for a new pandemic. Fortunately, this new virus, although very contagious, is only moderately virulent.

Can we control the new infectious diseases ?

Since mankind is not likely to stop changing its modes of life, and because micro-organisms will always retain their capacity of adaptation, new infectious diseases will most probably continue to emerge. What can we do to control them?

Fortunately, while the threat of infectious diseases was again imposing itself, science and technology made remarkable progress. This, in turn, permitted the development of new approaches to combat infectious diseases. This includes the search of new therapies, the development of vaccines, the extension of immunotherapeutic treatments or the exploitation of the information accumulated on the mechanisms of natural resistance in individuals endowed with an adequate genetic background.

Scientific progress already allowed us to stop two epidemics that could otherwise have been deadly. One was the mad cow disease (BSE), with its human equivalent, the new variant of Creutzfeldt-Jakob disease, and the second was the severe acute respiratory syndrome (SARS).

BSE resulted from a generalization of a practice that existed since the 1830s and consisting in feeding cattle with meat and bone meals (MBM). It was probably the large scale application of this practice to calves, a British specialty, that caused the initiation of this crisis at the end of the 1980s. Fortunately, research on spongiform encephalopathy, which started during the 18th century with the study of scrapie, led just on time to the prion theory at the end of the 1980s. Retrospectively, we were extraordinary lucky that a research that had lasted for two centuries reached maturity precisely when the first human cases appeared, thereby allowing us to take the measures allowing us to stop the epidemic before it had time to take dramatic proportions.

As for SARS, it is Internet that was at the centre of the counter offensive that permitted to "nip the epidemic in the bud". We all remember how this deadly pneumopathy that could rapidly be attributed to a corona virus appeared in Asia in 2003 and then started to spread worldwide. The understanding of the mechanisms of contamination, especially in the Metropole Hotel in Hong-Kong and in the hospitals where the first patients were treated, immediately communicated by Internet to health specialists all over the world allowed them to put in place adequate measures of surveillance and of isolation of the patients, in such a way as to break the chain of contaminations.

But now, let us examine some of the tracks that scientists follow to face this comeback of infectious diseases.

Towards an "intelligent" search for new anti-infectious agents

Most of the anti-infectious molecules that are used today were discovered more or less fortuitously. That was the case, for instance, for penicillin and quinine. In all of these cases, the target of the anti-infectious agent, i.e. the enzyme inhibited by this agent, was only identified much later. Today, the hope is to follow the reverse track, i.e. to identify first possible targets, and then, in a second step, to look for molecules that might act on these targets. Theoretically, this new approach, made possible because of the development of genomics, proteomics and structural biology, should widen considerably the scope of potential anti-infectious agents. The development of anti-proteases in the treatment of AIDS or that of oseltamivir in the treatment of flu was the result of such an approach.

New approaches in vaccinology

Vaccines offer the best prevention against infectious diseases. They usually consist of attenuated living microbes, of killed microbes or of molecules originating from microbes, the latter being often called subunit vaccines. Their administration simulates an infection, such that the immune system learns to mount a defence against the corresponding virulent microbe in case it would later encounter it. In the conception of new vaccines, scientists make use of new technologies.

For example, in the search for a vaccine against AIDS, several kinds of recombinant viruses have been constructed, in which HIV genes have been inserted into the genome of a harmless virus. This recombinant virus, a *bona fide* genetically modified organism, is expected to induce an immune reaction against HIV. One such virus was present in the first AIDS candidate vaccine to give promising results as tested recently in Thailand.

The development of immunotherapy

There are two main kinds of immunotherapeutic interventions.

The first kind, serotherapy, also called "passive" immunotherapy, consists in injecting to the patient antibodies directed against the microbe responsible for his illness. Discovered by scientists from the Pasteur Institute in 1894 to combat diphtheria, it consisted initially in the injection to the patients of serum from horses that had been previously immunized with diphtheria toxin. Although it represented the first successful attempt to stop an infection, this procedure was not without danger. Indeed, it could induce a strong and sometimes fatal reaction against the proteins of animal origin present in the serum (anaphylactic reaction). However, interest is renewed in this approach because it is now possible to inject purified antibodies of human origin, much less dangerous and which can be obtained from the culture of immune cells from a convalescent individual. There is progress along this line in the possible cure of flu and of infections with the *Chikungunya* virus.

The second kind, the so-called "active" immunotherapy, consists in a stimulation of the immune system to help it mount a defence against a microbe that has already started an infection. The spectacular progress accomplished in the understanding of the immune system makes such an approach feasible. The hope is not

only to help the organism fight an infection, for instance by HIV, but also to reject tumours.

Genetic control of infectious diseases

The existence of genetic factors in the susceptibility to infectious diseases has been known for a long time. The first well studied example was that of the resistance to malaria resulting from a mutation in a gene for haemoglobin (sickle cell disease).

Cases where a single mutation was shown to result in a significant degree of resistance to an infectious disease are rare. Still, one deserves to be mentioned because it resulted in the conception of a new antiviral agent. In the middle of the 1990s, a study of individuals who remained seronegative for HIV in spite of repeated exposure to the virus over several years revealed that their T4 lymphocytes, the class of cells where the virus normally multiplies preferentially, was lacking a molecule serving as a co-receptor for the virus. The idea then occurred that an inhibitor of that molecule might interfere with HIV infection. This led to the conception of a drug which is now used in AIDS treatment.

More generally, one hopes that the study of natural mechanisms bestowing resistance to an infectious disease may open new avenues in the treatment of this disease.

Surveillance

A very efficient organization for epidemiological surveillance is presently operational, mainly under the auspices of international organisations such as WHO. Its efficiency was greatly improved due to the development of electronic communication, such that any unusual phenomenon relating to human or animal health is immediately transmitted to specialists worldwide, thus allowing an early control of possible epidemics. The early control of SARS provided a demonstration of the efficiency of these procedures. This surveillance can still be improved, and it will be.

However, it would be even better to prevent the very emergence of infectious diseases. Several steps have been taken in this direction, by putting in place a surveillance of the environment, where the microbes of possible future epidemics are lurking. Hence, for instance, the surveillance of bird populations that may harbour dangerous influenza viruses. Hence, also, the surveillance of non human primates among which a high mortality rate may signify the emergence of Ebola type haemorrhagic fevers. An example for vector borne infectious diseases is the anticipation of Rift valley fever epidemics in certain regions of Africa by monitoring by satellite the changes in humidity, announcing an increase in the population of insect vectors.

Still, much remains to be done in improving this microbiological surveillance of our environment.

Control of the populations of insect vectors

The transmission of many dangerous microbes relies on arthropod vectors. Furthermore, vector borne diseases are the most likely to be affected by the ongoing climate change. Therefore, it is of special importance to develop efficient techniques to reduce either the populations of vectors, or their ability to transmit diseases.

Since the discovery of the insecticidal properties of DDT, chemical insecticides have been of great help to control the extension of epidemics of several vector-borne diseases such as malaria. Later, because chemical insecticides have their limits, biological insecticides were also developed, based mainly on the use toxins produced by entomopathogenic bacteria. These, however, also have their limits, such that entirely new techniques are being developed, including attempts to replace indigenous populations of vectors by genetically engineered strains unable to transmit the microbe.

Conclusion

Although the emergence of new infectious diseases is not really a new phenomenon – confer for instance the epidemic of black plague in Europe during the fourteenth century – there is something special about the cases of emergence that we have witnessed recently. First, they are much more frequent : an average of one per year according to WHO. Second, they do not always correspond to the transport of a disease from one region of the world to another, but often to the appearance of a disease never seen before, such as AIDS, for instance. And, as we discussed, these phenomena of emergence may result from the action of man, the adaptation of the microbes, or both.

Fortunately, as we have seen, while the great comeback of microbes was on its way, science made such a spectacular progress that a victorious counter attack of mankind is far from excluded. However, the example of AIDS is here to remind us that we haven't won yet. Therefore, we should remain on our guard and support research on infectious diseases and the training of experts in the many disciplines concerned, including those that were unfortunately neglected over the past 20 or 30 years, such as ecology and medical entomology.