Biodiversity and Emerging Diseases

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ABSTRACT: First we remind general considerations concerning biodiversity on earth and particularly the loss of genetic biodiversity that seems irreversible whether its origin is directly or indirectly linked to human activities. Urgent and considerable efforts must be made from now on to catalogue, understand, preserve, and enhance the value of biodiversity while ensuring food safety and human and animal health. Ambitious integrated and multifield research programs must be implemented in order to understand the causes and anticipate the consequences of loss of biodiversity. Such losses are a serious threat to sustainable development and to the quality of life of future generations. They have an influence on the natural balance of global biodiversity in particularly in reducing the capability of species to adapt rapidly by genetic mutations to survive in modified ecosystems. Usually, the natural immune systems of mammals (both human and animal), are highly polymorphic and able to adapt rapidly to new situations. We more specifically discuss the fact that if the genetic diversity of the affected populations is low the invading microorganisms, will suddenly expand and create epidemic outbreaks with risks of pandemic. So biodiversity appears to function as an important barrier (buffer), especially against disease-causing organisms, which can function in different ways. Finally, we discuss the importance of preserving biodiversity mainly in the wildlife ecosystems as an integrated and sustainable approach among others in order to prevent and control the emergence or reemergence of diseases in animals and humans (zoonosis). Although plants are also part of this paradigm, they fall outside our field of study.

KEYWORDS: biodiversity; emerging diseases; immunogenetics; breeding intensification

"Human beings modify the environment and the environment modifies part of human beings directly dependent on environmental change."
(Jiddu Krishnamurti, 1934)

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INTRODUCTION

The earth is host to a vast biological diversity that includes greater than the millions of known species, a wealth of genomes, physiological mechanisms, and behaviors. This biological diversity of plants, animals, and microbes creates a complex ecosystem comprising a diversity of individuals and populations. These various levels of diversity are the result of over 3 billion years of continuing evolution, and are an important chapter in the earth's geological timeline. Fewer than two million of the estimated 30 million species have been described, of which 75% are invertebrates. Although biodiversity changes over the long term, man is coming to the realization that many of his harmful actions on the environment have had unprecedented effects on the distribution and number of living species, the stability of ecosystems, and the genetic drift and natural evolution of organisms. The current loss of species rate is notably higher than the natural rate of extinction. Moreover, tens of thousands of other species are already condemned to extinction in a term on a human timescale, largely due to the destruction of habitat across the globe. This loss of biodiversity is caused mainly by economic and demographic factors, and especially by the increasing demand for space and biological resources needed to sustain global production and the growth of human population, its consumption, and its trade. Furthermore, we are currently witnessing the loss, fragmentation, and degradation of natural habitat through the overexploitation of biological resources, the introduction of exotic species, soil, water, and atmospheric pollution, and more recently through the first signs of global climate change. The loss of genetic biodiversity seems irreversible whether its origin is directly or indirectly caused by humans. Ambitious integrated and multifield research programs must be implemented in order to understand the causes and anticipate the consequences of loss of biodiversity; *in fine*, their purpose would be to put forward rational strategies for the preservation of biodiversity. On a more general level, such losses have an influence on the natural balance of global biodiversity: "nature hates a vacuum" and manifests itself by systematically replacing destroyed spaces and extinct species with new organisms, which in turn invade and change the environment, adapt rapidly in order to survive, and more often than not, transmit this in their genotype and thus perpetuate this transformation (e.g., genetic mutation). Such "forced" mutations can be silent and without major effects on individuals, ecosystems, or their inhabitants. These changes can have a strong effect on individuals, which may evolve to have increased pathogenicity or fertility, etc., . . . and affect the functioning of an ecosystem, with severe consequences for the other species living within the same ecosystem. For example, from a medical perspective the crossing of species barrier may inflict a new (emerging) parasitism on an unprecedented host, or escaping natural defense mechanisms. However, if the genetic diversity of the affected populations is low (e.g., inbreeding in small populations that are isolated or fragmented, monoclonal populations bred in industrial farms, etc.),

the invading microorganisms, will suddenly expand and create epidemic outbreaks with risks of pandemic. Such conditions provide the opportunity for emerging and reemerging diseases, with often severe clinical syndromes and epidemic outbreaks that can be devastating for animals as well as for humans (zoonosis) living in shared ecosystems or in overlapping territories (sympatry). Many pathogens thus threaten humans and domesticated animals when their own natural habitats have been disturbed. In such a context, the interactions between pathogens, the hosts' immune system (human and animal), resistance to drugs, and the density of human and animal populations can cause exotic species to become invasive to hosts without previous exposure or immune response. Inversely, exotic (exogenous) species can introduce pathogens that threaten the local endemic species.

Biodiversity thus appears to function as an important barrier (buffer), especially against disease-causing organisms, which can function in different ways. For example, the polymorphic major histocompatibility complex (MHC) that protects a population or as a dilution effect on pathogens when populations are diversified. This is the case for pathogens transmitted through vectors, such as malaria, sleeping sickness, or West Nile fever, whose vectors turn feed on humans and domesticated animals when the biodiversity of wildlife is restricted.

WHAT EXACTLY IS MEANT BY THE TERM BIODIVERSITY?

Biodiversity involves the entire diversity of the living world, from the very large (natural landscapes) to the very small (genes), and extending from the diversity of ecosystems (oceans, forests, cultivated plains, or desert areas) to the diversity of genomes with their organizations and functions. Biodiversity encompasses the diversity of all living species, including microorganisms (virus, bacteria, prions, rickettsia, parasites, and fungi), algae, plants, and animals, and of their biology, which are all regulated by climates and environments. Biodiversity is therefore a reflection of the manifestation of the differences between living entities (species, populations, individuals. . .) and of the ecological interactions within which species evolve.

It is very difficult to give a precise estimate of the number of species living on the planet. The evaluation bracket is very wide and varies between 5 and 100 million depending on the author. Of the average figure most commonly used of 30 million species, less than 2 million have been described and 75% of these are insects! If one takes into account the fact that each species has at least one species-specific parasitic species (e.g., Wolbachia in insects), this estimate of undescribed species would probably exponentially outnumber "visible" species.

Biological diversity (biodiversity) is descriptive (static) as well as evolutive (dynamic), if one takes into account the totality of interactions and variability

of living beings in a heterogeneous and changing world. By interactions, we mean such phenomena of global change, such as climate change, which has a multitude of causes and consequences on the environment.[1] The history of planet earth is made up of a succession of climatic changes, and we are currently going through the sixth great planetary extinction crisis, with a rate of extinction 100 times higher than the average natural rate. Every day, several living species, mostly unknown to us, disappear from the earth. IUCN (World Conservation Union) has published a "red list" of over 7000 known threatened species[2] within the animal kingdom alone, and 25% of the mere 4600 described are threatened with extinction in the relatively short term. (http://www.iucn.org/themes/ssc/red-lists.htm).

The *variability of biodiversity* is largely due to gene mutations (genetic variability), which are random, mostly adaptive and self-preserving, and which allow all organisms to adapt and survive in constraining environments. Without constant and necessary modifications these species would be doomed to extinction.

Genes of epigenetic origin may also play an important role in the evolution of living beings, especially in the transmission of acquired characters, as well as using other evolutionary mechanisms outside of classical Mendelian genetics. This natural (genetic) selection is the theory of the evolution of species as initially developed by Darwin in 1859. Population is the unit of evolutionary change from which diversity originates. Indeed, the evolutionary processes, which maintain organisms in the realm of the living, or the ecological processes, which precipitate them toward extinction, operate at this very level of organic integration.

Local populations and their wealth of genetic diversity must be the focus of our greatest attention, in particular through preservation action. Preservation of biodiversity through the interactions between species and their natural environment has a considerable potential for the evolution of the planet, and one, which must be sustainable so as to allow adaptation and survival in the face of planetary changes. The environment's space–time dynamics is the force, which causes the emergence of species, safeguards their existence, or suddenly causes them to die out forever. This driving power at the heart of biodiversity manifests itself through all sorts of changes, which may be violent, as in the case of accidents and disturbances (natural disasters, storms, fire outbreaks, floods. . .). Less brutal changes to their own environment may be caused by the organisms themselves, and especially humans.

Humans have been interacting with their environment since the Paleolithic era over 12,000 years ago.[3] At first humans evolved in small family groups in very open ecosystems and lived primarily from hunting and gathering. Populations progressively formed villages and domesticated several animal species, as depicted in cave paintings. Such cohabitation between humans, as well as between humans and animals, has influenced both social and health issues.[4] Between 70% and 80% of infectious diseases present in humans have been

shown to be of animal origin.[5] Some of these were acquired in the Neolithic era when the first sedentary societies were organized and humans began to practice agriculture and farming using domesticated animals that were once wild. Throughout his history, *Homo sapiens sapiens* has successfully eliminated predators and competitors; however, the same cannot be said for his parasites and pathogens. It is impossible to make even a rough estimate of the number of micro- or macroorganism species that have the potential to be pathogenic for human or animal populations. In human or animal populations, those individuals most susceptible to diseases die, while only those resistant will survive.

Demographic changes have gradually altered living conditions on earth. Today man finds himself responsible for situations far less propitious than ever, which are evolving rapidly. Pollution and the destruction of ecosystems are escalating. Demographic explosion, especially in developing countries, causes increased demand on food supplies of both vegetable and animal origins. Large concentrations of human and domesticated animal populations in the form of megalopolis and breeding units are growing in density with far-reaching consequences for the environment, especially the management of natural (human and animal) and industrial wastes. Contact between human beings, as well as between humans and animals, is increasing both in duration and intensity.[6] Among other things, ongoing contact due to overpopulation and overcrowding causes stresses, which induce discomfort and biological dysfunctions, especially of a physiological nature. Immune defense systems are often disturbed; giving way to the emergence of new (emerging) diseases, or diseases that were thought to be under control or eradicated may reemerge.

Epidemics have increasingly severe consequences and result in greater morbidity and mortality. Industrial farming, with several thousand individuals from the same species and often from the same genetic strain (clone), causes considerable loss of genetic diversity. Epidemics that arise from this environment can then become destructive, as was evidenced by the avian influenza epidemic in Taiwan and more recently in southeast Asia. Pandemics therefore will likely become more frequent and will be enhanced by international trade, especially through air transport. The incubation period of all infectious agents (virus, bacteria, or parasite) is longer than the length of time needed for an individual carrying the germ (with no clinical signs) to fly anywhere on earth, and a pathogen could contaminate the entire planet in less than 24 h.

WHAT IS MEANT BY EMERGING OR REEMERGING DISEASES?

The lightning spread of severe acute respiratory syndrome (SARS), unprecedented in its speed and scope, was a reminder of man's vulnerability in the face of constantly evolving infectious diseases. The current avian influenza epizooty, which once again poses threat to world populations, highlights the

magnitude of social damage, and economic loss. For the past few decades, health specialists worldwide have been confronted with emergence of viral fevers, identification of pathologies linked to previously no described germs as well as with the overwhelming worldwide spread of acquired immune deficiency syndrome (AIDS). The increasing numbers of epidemic phenomena, which appear in specific epidemiological contexts, and which imply previously no described human risk (dams and water-related diseases; deforestation and zoonosis acquired through contact with wild animals) have led the scientific community to assess these infections and to research and define the concept of new or emerging disease associated with risk factors.[7]

While emergence of new diseases appears to be linked with human behavior, natural changes in the environment must also be taken into account in this analysis (e.g., health issues caused by supraseasonal climate trends, El Nino, global warming, degradation of the ozone layer). The serious risks of emergence of infectious diseases in general, and zoonosis in particular, justify the need for integrated studies with multifield scientific approaches. Whether in the northern or southern hemispheres, identification of factors and areas of disease emergence need to be defined, along with the fundamental mechanisms that result from environmental changes previously not described of natural or human origin. A broader knowledge of emergence factors linked with human, animal hosts (mammals), or vectors/vector-borne pathogens, will allow for definition risk factors that will provide a basis for designing prevention and control strategies. Genetics (phylogenies) research on arthropod vectors and studies on bioecology of hosts and pathogens coevolution are also much needed.

The concept of pathocenosis[8] can be developed when the interaction of pathogens and the events that lead to epidemization are defined. Prediction of outbreaks could then be made by modeling the emergence and diffusion of diseases, in relation to the balance of biotopes, and emergence of invasive species that result from extinction or suppression of populations, pathogens, or hosts.[9] Evolutionary biology (of hosts and parasites) as much as human and social sciences concerned with the evolution of societies are the domains in which this research could be conducted and where emergence intervention/prevention system could then be applied.

Our ability to understand the dynamics of emergence is tied to the following essential questions. Where do pathogens come from? Is it possible to detect pathogens with the potential for emergence? What are the conditions (macro- and microecological) that pave the way for their emergence? Under which conditions do they spread and exactly what role do pathogens play in ecosystems? What are the tools and administrative and scientific strategies needed in order to detect the antecedent occurrences that precede an epidemic? What mechanisms could explain the increased virulence of pathogens and which genetic modifications could explain emergence of virulence in previously nonpathogenic organisms? Are specific elements of a pathogen's genome responsible for all or

part of this virulence? Is increase in virulence always associated with change, or with a transfer of populations or host species?

Study of pathogens' influence on host populations has demonstrated that their effect is significant.[10,11] Many studies have been conducted on the regulatory role of parasites and pathogens in human and animal populations, primarily because they are directly related to public and veterinary health. However, the impact of pathogens and parasites on the functioning of ecosystems is an area of research that has been ignored, despite the fact that pathogens are everywhere and represent a large proportion of the living world.[12] Moreover, pathogens play a very important role in preserving the balance of ecosystems by acting as regulators or "deregulators" of the ecological balance that has been established over time. Some of the answers to numerous human and animal public health issues, for example, resistance to antibiotics, require a better understanding of the ecology of pathogenic organisms and both their populations and species community. In the future, understanding this multispecies dimension will be essential.[13]

IMMUNOGENETICS, LOSS OF DIVERSITY, AND RISK OF EMERGENCE OF DISEASES

As we have established, description of all the scientific approaches that each take into account a different facet of biodiversity would be tedious and exhausting. We will limit our discussion to the "immunogenetics" aspect that essentially controls the mammal host immune defense mechanisms. The overall question could be stated as follows: *In terms of health, what are the risks and what could be the consequences, particularly at the host–pathogen interface, of the loss of genetic diversity (biodiversity) in the emergence or reemergence of infectious diseases?* Defense mechanisms at the host–pathogen interface involve both the host (mammal or arthropod) and pathogen. Defense mechanisms could include physical (skin's natural tissue barrier, mucus, cilium. . .) or biochemical nature (enzymatic action, fever. . .) to prevent infection/infestation by pathogens. The pathogens could also activate biochemical neutralization mechanisms or physical or molecular mimesis that would allow them to escape/circumvent the host defense mechanisms. If the pathogen manages to escape those initial defenses and penetrates inside the host, the host may deploy several cellular and molecular biochemical mechanisms and activate several nonspecific and specific immune defense systems to destroying/suppressing the totality of pathogens. In turn, pathogens may activate escape mechanisms, including genetic mutations that bypass the host-specific pathogen recognition functions. A successful parasite does not kill its host, which would jeopardize its survival. Finally, arthropod vectors, such as hematophagous fleas, ticks, and mosquitoes, have defense systems against pathogens that effect regulation of the parasite's diffusion and multiplication and the host, who contributes to the survival of the vector population with the blood meal (physical avoidance,

chemotaxin, "bite" strategy). A more detailed look from a genomic perspective at these mechanisms at the host–pathogen interface reveals that many of them interact so as to perpetually neutralize each other, and that this opposition is all the more balanced if the hosts' genetic diversity is high enough to respond to that of the pathogens. In fact, the higher the hosts' genetic diversity, the greater the probability of neutralization/equilibrium. If genetic diversity were to decrease, the hosts would no longer be able to control the pathogens' genetic diversity adequately or correctly. The pathogens would develop relentlessly in the host population with various consequences for the latter, which could reach total extinction in the short to long term. Preserving current biodiversity means safeguarding its future evolution potential, a future as yet unknown to us since, although some repetition of the past is possible through DNA's and paleontology's archives, future prediction is not. Most importantly, evolution never turns back the clock: this irreversibility is the very cause of the irrevocable mechanisms of the extinction of species.

HOST–PATHOGEN GENOMICS AND IMMUNOGENETICS

We know all species are part of the chain of living beings whose remarkable unity expresses itself through the biochemical and genetic medium of DNA. DNA is like a "software," a sort of "unbroken link," a memory of the living world from the time of the species emergence. DNA is the universal code common to all plants and animals, a stock of information, the foundation of biological diversity, and the primary material on which evolution relies to maintain the species in a state of adaptation allowing them to resist environmental change. The majority of pathogens (prokaryotes) possess genomes that are smaller (between 10^3 and 10^7 base pairs [bp]) than those of their eukaryotic hosts, whether mammal or bird (3.10^9 bp). Prokaryotic pathogens have a genome whose DNA is almost 100% encoding, but the same does not apply to the genomes of mammals, in which only 10% are functional protein-encoding genes. The other 90% consist of noncoding sequences, introns, regulatory sequences, pseudogenes, etc. Random mutations occur every 10^6 bp during each DNA replication (cell division). This statistically means that the majority of mutations in prokaryotic pathogens occurs in encoding areas and has direct functional consequences. Inversely, the frequency of mutation every 10^6 bp, in relation to the 10^9 bp size of eukaryotic genomes, will cause a majority of mutations to occur in noncoding zones (silent mutations) and will accordingly have no direct functional consequence. Having considered this, it is apparent that pathogens' genetic mutation and, therefore, adaptation potential are far superior to those of the hosts. Moreover, replications occur during cell division and reproductions, and pathogens' reproduction cycles are considerably shorter than those of higher mammals, including man. In brief, the rate of mutation and therefore of genetic variability is much greater in prokaryotes

than in higher eukaryotes. It grants them a considerable ability to adapt to their environment rapidly, especially by escaping the hosts' immune defense mechanisms by masking or molecular mimesis. Mammal hosts respond to the pathogens' large variability potential with genetic systems that are more complex, highly polymorphic, and with a large number of genes whose rearrangements allow for a considerable number of molecular combinations. Consider the example of the MHC, and in particular its class I and class II molecules involved in immune recognition mechanisms at an extracellular and intracellular level respectively, and the five different types of immunoglobulin (antibodies) IgA, IgE, IgD, IgG and IgM (http://imgt.cines.fr). All these structurally close molecules are made up of proteins with constant and variable chains encoded by a very large number of genes. MHC molecules are encoded by several dozen loci distributed across one or several chromosomes, and each of these loci presents several dozen different alleles. Immunoglobulin molecules are encoded by several hundred genes whose recombinations can statistically produce over 10^8 possible rearrangements. Taking only into account these two immune defense systems—MHC molecules and immunoglobulin—we begin to get a grasp of the mammal hosts' incredible reactivity potential, both in terms of speed and specificity, to recognize both the exogenous and endogenous antigens of pathogens and to deploy control and suppression processes immediately. Suppression of the host's pathogens must be complete, otherwise the few "surviving" (i.e., unsuppressed) pathogens can adapt rapidly through mutation and once again escape the hosts' specific defense systems or chemical treatments, as in the case of bacterial antibiotic resistance or chemoresistance mechanisms of parasites. Moreover, as the genetic system of mammals is autosomal with codominant expression and possible gene duplications, heterozygoty further multiplies allelic variability, which allows for the increase of the hosts' immune reactivity potential. This particular benefit of heterozygoty allows the hosts to adapt to the mutational capacity of pathogens. Inversely, any decrease in the hosts' genetic variability, whether at individual or population level (homozygoty, consanguinity rate, bottleneck, etc.) considerably reduces immune reactivity and the hosts' ability to control and suppress pathogens. Similarly, considering monospecific populations rather than individuals, Apanius[14] developed the theory of frequency-dependent coevolution of cyclic and antagonist mechanisms between a given pathogen population and a host population (FIG. 1). Taking the case of an equilibrium situation in which a host population shows a high frequency of a specific MHC allele, which strongly correlates with a given character, such as for instance resistance to a given disease. If the pathogen responsible for this disease manages to rapidly circumvent the host's immune defenses through mutation, a number of individuals within the host population will perish and the frequency of the "circumvented" resistant allele will decrease in the host population. Its proportion will thus progressively decrease in the overall population until a genetic rearrangement occurs in an individual from the host population, allowing it to control the

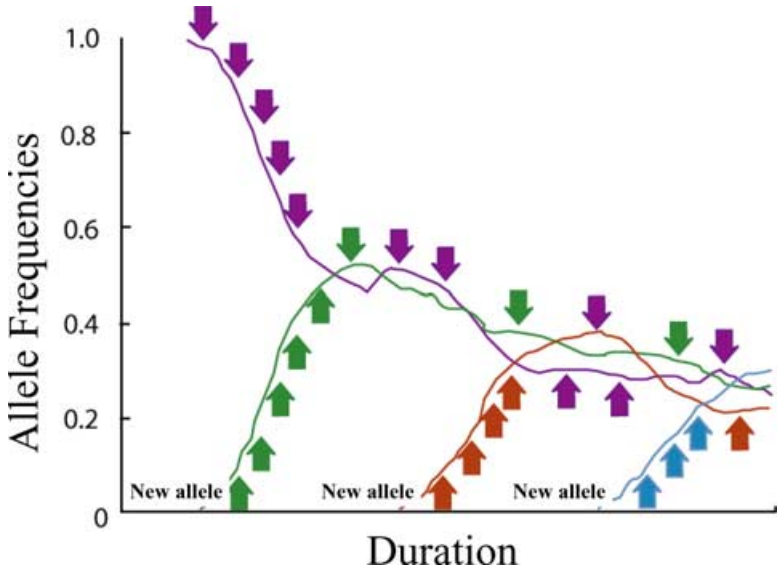

FIGURE 1. Frequence-dependence Apanius' theory on the cyclic and antagonist mechanisms of coevolution at the host–pathogen level populations.

pathogen's new variant. Natural selection eradicates sensitive hosts and only individuals having the new resistant allele survive. By reproducing, these individuals will cause the frequency of the new resistant allele to increase in the population, which will in turn see its numbers grow. Escape/circumvention by pathogens and genetic rearrangements in the hosts are constant and antagonist cyclical mechanisms at the host–pathogen interface, which occur over the time span of several generations of hosts. Each time the pathogen succeeds in circumventing the host population's defenses through mutation, the latter's probabilities of survival will be proportional to its genetic diversity. Indeed, the greater the gene diversity in a host population, the greater the possibilities of genetic rearrangements, the more the host population will be able to control pathogen infections/infestations cyclically and the greater the probability of survival over time. In the opposite case, it will eventually become extinct in the more or less short term as its reproduction cycles will not be sufficient to rebuild population equilibrium (i.e., population critical mass). The notion of population critical mass is essential for the understanding of relations between the host and the pathogen biological diversity (dilution effect, buffer effect), and of the probability of lateral transfers to other host species, including humans, by crossing of species barrier. In reality, mechanisms described for a given disease are much more complex, since pathogens' aggressions are manifold and often simultaneous and correlations are variable; one allele providing resistance to one specific disease can also be associated with greater sensitivity

to another disease. One example would be hosts "tolerant" to a germ, which thus protects their population (i.e., the germ does not exert its pathogenicity on its natural host and its host does not recognize it as "immunologically" foreign). The germ, although potentially pathogenic for hosts other than its natural host, endures in the surrounding ecosystem without any visible damage to the community. Only emergence brought about by specific conditions will disturb this apparent equilibrium (pathocenosis).[8] This example is also played out as described above, according to constant interactions whereby natural selection through the rapid suppression of the most sensitive individuals will tend to reduce genetic diversity through the loss of sensitivity alleles on a population scale. Inversely, the hosts' gene rearrangements will preserve diversity. The rate of evolution of mutational frequencies is obviously highly variable in mammals and will depend on linkage disequilibrium in linked genes, on selective pressure on the various genetic systems taken into account, on the type of mutation (deletion, substitution, or insertion), their rate, and whether or not they are located in functional genomic areas. Human activity disturbs, interferes with, and often thwarts the cyclical mechanisms of natural equilibriums through breeding techniques, such as marker-assisted selection (MAS), or through chemical treatment (more or less adequately controlled use of antibiotics or antiparasitics). Hence, selection mechanisms can occur simultaneously within individuals, given groups or entire populations, with variable reactive time spans. The greater a population's genetic (gene) diversity, the greater the chances of survival of its individuals and the more sustainable will be the survival of its population.

BIODIVERSITY AND BREEDING SYSTEMS

Humans have developed a vast number of animal breeding methods that have varied greatly since the initial domestication of several animal species. We will only analyze the immunopathological risks associated with loss of biodiversity in modern industrial breeding farms, with regards, for example, to the latest great viral and bacterial epidemics, whether porcine or avian. The large concentration of animals farmed in overcrowded conditions in industrial batteries (several hundreds or even several thousands of individuals in a confined space), provides an extremely infectious context through contact with numerous pathogens, as opposed to natural extensive or semiextensive breeding conditions. This effect is enhanced when new species are added to an intensive monospecific breeding farm (e.g., poultry/porcine) whose overcrowded conditions will foster anomalous exchanges and cause a major risk of epidemic by crossing of species barrier. Where a small infectious dose would naturally be controlled by a normal immune system, there is no chance, even for an efficient immune system, of controlling huge infectious doses which "saturate" defense effector mechanisms and "overflow" the animals'

immune mechanisms, all the more so when the animals are descended from consanguineous genetic strains (clones) with a high rate of homozygoty and therefore low genetic diversity, which reduces their immune reaction capacity. The "infectious dose effect" is an important factor for consideration, since the rapidity of emergence and magnitude of an epidemic, as well as relapse episodes (emergence) triggered by pathogens with high mutational potential, all depend on it. Important questions are: Where do the pathogens provoking epidemic outbreaks come from? Are they new (emerging) or do they reemerge (reemerging) through certain particular breeding or environmental conditions? Do they come from food? Do they originate in new and infected individuals, or from contact with wild animals, such as rodents? It is difficult to answer such questions. What we do know is that wild fauna is generally well adapted to its pathogenic environment through natural selection but that this is absolutely not the case for farmed individuals, whose contact with wild pathogenic strains always has severe pathological consequences. Many examples of pathogen transmission either direct or through vectors (West Nile Fever, blue tongue disease, malaria, trypanosomiasis, etc.), have demonstrated the real risks of such contact between wild and farmed environments, which should to a minimum. Domesticated hosts' genetic (bio)diversity is, however, an important factor, a type of protective barrier (buffer) against emerging and reemerging diseases. For example, the introduction of exotic genotypes in a specific environment, whether directly or by cross-breeding of exogenous genotypes, is a serious mistake. First, it presents a major risk of reducing the genetic diversity (with a weakening of immune defense capacities) of local populations often perfectly well adapted to their environment through natural selection (including resistance to endemic pathogenic strains); it also carries a major risk of introducing pathogenic strains unknown to the local population and which might provoke pathological outbreaks that can lead to the rapid extinction of endemic species. The extinction of endemic populations allows the exotic species to become invasive, which can induce huge environmental changes involving the emergence of ecosytemic disequilibrium. Will depleted ecosystems withstand the aggressiveness of invasive species whose worldwide threat is increasing as it becomes intensified by global trade? Will the extinction of certain species known as "key species" provoke the domino effect extinction of dependent species and cause a complex reorganization of ecosystems?[15] Will ecosystems be steered into new, detrimental directions, which would remain stable once certain irreversibility thresholds have been reached? Will we witness breakages of interactions between species in such diverse areas as competition, predation, and parasitism as well as all types of symbiosis? Will we observe new power relations in the never-ending "arms race" between pathogens and hosts, which could provoke the emergence of new pathologies or the reemergence of old ones we hoped had been suppressed. Indeed, if certain natural habitats disappear, especially wild ones, the absence of their usual wild hosts may cause pathogens to leave their ecosystem, and colonize and threaten domesticated

environments or populations sensitive to them. The risks of emergence of new epidemic outbreaks are thus increased and threaten animals and humans alike (zoonosis) in the case of transmission by crossing of species barrier.

CONCLUSIONS AND RECOMMENDATIONS

Returning to a veterinary context that takes into account the various elements in this article, we can suggest what should be avoided in terms of breeding techniques, especially within sustainable and rational intensification; we can also make some concrete recommendations in order to avoid, or at least control, the emergence or reemergence of diseases including zoonosis. Human demographic evolution is evidently at the heart of the problems we are currently experiencing. Human penetration into new territories for the purposes of establishing new species, agriculture, farming, and for the tourist exploration of still untouched natural ecosystems, increase the probabilities of contact and therefore transmission of pathogens from unsuspected reservoirs or vectors.[16] Two interactive configurations must be taken into account: on the one hand, the worldwide growth of human population, and on the other hand biodiversity, a great part of which is the source of past, present, and probably future diseases. The central problem concerns demographic relations between human and other species. The more human population will grow, the more this population will compete with other animal species, increasing the risk of contacts with potentially dangerous agents it had not been previously confronted with.

Another aspect is one of relations between geographical areas. Countries in the intertropical zone are host to 30 to 35 times more infectious and parasitic agents currently responsible for diseases in human populations than temperate countries.[17] Yet to this day, huge numbers of microorganisms remain unknown in tropical regions where it is estimated that hardly 10% of biological diversity has been cataloged. We can only predict the number of pro- or eukaryotic organisms, which could be pathogenic to their new hosts when transmitted to human, animal, or vegetal populations. Modern societies could be incurring great risks by allowing the scourge of poverty to spread over the populations of the south.[18] As for the intensification of farming systems, which in the south even more than in the north, responds to the increasing demand for animal food products associated with human demographic growth, it should be sustainable and rational, and take into account a whole set of environmental (medical measures, effluent management. . .), sociological, and economical as well as genetic factors, as previously seen. We must avoid noncontrolled farming, as well as large, highly populated industrial breeding farms that generally use animals from the same species, the same origin, or even from monoclonal strains, which lead to a detrimental loss of genetic diversity. The numbers and density in which animals are bred result in overcrowded conditions, which, among other things, stress the animals, modify their metabolic performances,

weaken their immune system, and above all maintain a high risk of hyperinfection by massive infectious loads. We should also avoid multispecies breeding (chicken, ducks, or pigs for example) within the same industrial farm or the same geographical zone: if a disease breaks out, there is a high risk of mutation/recombination/reassortment of pathogens and thus of crossing the species barrier. This is also the reason why contact with humans and especially breeding farm employees should be avoided as much as possible when a disease breaks out on an industrial farm; this can be achieved by applying strict rules on movement restriction and on the use of mechanical (masks, protective suits) and chemical protection (various disinfections, preventive vaccination). Such measures are generally already recommended by public services (OIE, WHO, relevant ministries), but are not always correctly implemented. In case of epidemic, stringent controls are required at all stages of the production pipeline. Possible alternatives that would reduce the risks of contact could for instance include replacing large industrial units with several smaller-scale production units containing lower densities of animals.[19] In other words, this means favoring product quality over industrial yield. There are many advantages to this: animals would be less stressed and thus more resistant to infectious aggressions; contact between individuals would be less intense, which would reduce infection rates since infectious doses would be lower. It would thus be possible to diversify the races bred in farms containing several mid-sized breeding units by using different animal strains for one species. Genetic diversity would be maintained and allow for a variable immune behavior in the face of infection/infestation by pathogens. In case of epidemic, this would reduce the risks of high mortality and their disastrous economic consequences for farmers, since not all the animals would die (as is the case on large industrial farms). The surviving animals would thus be selected *de facto* to recreate a population resistant to the given pathogen. All players involved in the farming production pipeline, whether political, economical, or professional, should be aware of the importance of valorizing biodiversity through the diversification of animal strains used for breeding. Strains with different potentials and qualities would in turn diversify economic markets and offer a wider choice of products to the consumer.

Last but not least, we suggest the development of an increased number of research projects specifically aimed at wild environments and species. The evaluation and characterization of wild genetic diversity will provide a wealth of information and thus allow correct modeling and valorization of biodiversity on the basis of the natural adaptation and survival potential of wild populations.[11] Obviously, we should avoid contact between wild fauna, which is an important pathogen reservoir, and domesticated animals, which are not adapted and so are for the most part sensitive to those pathogens. Inversely, biological diversity acquired by wild fauna through natural selection should be valorized as having considerable potential for the future, especially from a genetic perspective. Species with amazing properties have been sorted through

natural selection. Many are still unknown to us and need to be discovered in order to be valorized. Although wild species act as pathogen reservoirs, they are also reservoirs of pathogen-resistant genes, more commonly of adaptation genes for various difficult or constraining environments (saline or desert habitat). Identifying such genes of interest would allow their introgression in domestic species with the use of various reproductive biotechnologies. We are convinced that the results of such research will in future contribute strongly to controlling the emergence of new diseases, or to the reemergence or spread of known diseases, by rational and sustainable farming of genetically resistant species.

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