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REVIEW

Infectious diseases in the 21st century: old challenges and new opportunities

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Summary Infectious diseases are the confrontation of two worlds, the microbial world and the world of human physiology. Although these two worlds are as a whole governed by the same laws of nature, they show substantial differences: the microbiological world is 1000 times older, and was initiated by the development of the archaea, the 'living organisms of the extreme': its biomass and its diversity are immense — two to three billion species or 60% of the total biomass of the planet. The number of pathogens that adapted to man, however, is extremely limited — barely 1000. Thus, over billions of years, an evolution of the microbial world took place from 'early life', characterized by chemosynthesis, to the 'modern pathogens', and entailed a dramatic 'concentration' of life conditions and an adaptation towards a narrow range of requirements — those allowing survival in the human body.

Within the last two centuries, these two slowly evolving systems, microbial life and human life, were profoundly modified in an unprecedented manner by a third player, human civilization, with its global impact on the environment through physical, chemical, societal, and climatic determinants. An appreciation of the evolution of infectious diseases in the 21st century and of the development of new diagnostic and therapeutic strategies therefore requires a full understanding of these three domains: human physiology, microbiology, and the environment.

This review will put major emphasis on the environmental role of civilization on infectious diseases before considering new opportunities to combat them through novel and creative solutions.

Impact of human civilization on the environment

The Greenhouse Effect

The distribution of gases in the earth's atmosphere — highly reactive O_2, H_2, CH_4, among others — is far from the balance predicted by physical laws alone.[1] As suggested by James E. Lovelock, life

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profoundly affects the earth's atmosphere, resulting in a close relationship between the atmospheric, geological and biological environments. These physical and biological considerations have their poetical counterpart in the development of the Gaia hypothesis (Goddess of Earth): the earth is alive, the atmosphere is its circulatory system, life optimizes its own environment in a cognisant way and through self-regulatory feedback mechanisms. What scientific evidence do we have that this interrelationship holds true?

Climate change, as currently observed through the global warming phenomenon, is exerting a profound influence on life, and therefore on infectious diseases, by changing their geographic distribution, demographic data, as well as vector conditions.[2] Climate, in turn is itself deeply influenced by the evolution of the greenhouse gases of the last 200 years.

Since 1800, the CO_2 concentration of the atmosphere has risen by 30%, whereas the nitrous oxides have increased by 20%, and methane concentration has risen by more than 100%. These changes affect profoundly the reflection and dissipation of solar energy on the earth's surface. All these effects, summarized under the general term of the greenhouse effect, have been intensified by additional water evaporation. Global warming is estimated at $1\,^{\circ}C$ per century. Although such gradual warming could be considered to be inconsequential, it is to be noted that the last glacial period with its dramatic consequences was due to a mere $5\,^{\circ}C$ temperature change.

Global warming has already had a marked effect on the planetary water and air cycles, as shown by a few examples:[3]

- The sea level has already risen by 35 cm since 1900, changing many demographic conditions and the epidemiology of many infectious diseases such as malaria, dengue and cholera
- As another example, the El Nino — the southern oscillation phenomenon which moves warm waters and rain to the Pacific coast of South America in a one-in-every-four year cycle has shown some amplification. Thus, the most rapid spread of the 1991 cholera epidemic in Peru along the Pacific coast, was associated with such a coastal warming. The 1994 Bangladesh cholera epidemic also closely followed the sea surface temperature fluctuations
- Other examples and threats include the Rift Valley fever epidemic in East Africa 1997—98, and the present dramatic geographic extension of dengue and malaria.

Urbanization, the development of megalopolis

In the last 50 years, the world's landscape has been profoundly modified by a vast and relentless societal movement from the countryside to the cities, as shown by the following numbers. It is considered today that 47% of the world's population is urbanized. By 2030, it will be 60% or 4.9 billion people. By as early as 2007, urban dwellers will exceed the rural population for the first time in history. This historical trend towards urbanization is particularly marked in the developing world. If in the industrialized countries, the number of megalopolis has been kept at 6 over 50 years, the number will increase from 5 to 27 in countries in development, creating totally new environmental conditions. This rapid urban growth puts a strain on the capacity of local and national governments to come up with adequate provision of water, electricity, sewage and social services. Historical scourges such as tuberculosis, hepatitis and sexually transmitted infections, and new diseases such as AIDS find ideal breeding conditions in this new, radically altered environment. An example of this dramatic situation is related to the problem of access to water: water is not only elementary to human life, it is also the ideal milieu for pathogen development and transmission. Access to drinking water and sanitation systems are still unsolved problems of humanity. It is estimated that by 2010, one third of humanity will not have access to this elementary life system and/or to adequate sewage systems. The fight for clean water could well become a major driving force of our globalized political system in the near future.[4]

World migration

Our transformed planetary ecosystem is permanently traversed by millions of people travelling. The World Migration Report 2000 from the International Organization for Migration gives some impressive numbers, regarding population movements across borders;[5] it does not take into consideration hidden problems of internal displacements and of illegal migrants; they are often victims of professional networks specialized in human trafficking, and are exposed to dramatic health conditions. A few numbers will illustrate this new epidemiology: the number of displaced people around the world reached 150 million by 2000, and this number does not take into account internally displaced populations — such as frequent during civil wars — nor does it take into account illegal migration, which accounts for many more millions —

close to 15. Although voluntary migrants are often spurred by economic motives, most refugees escape under precarious conditions such as human violence or natural catastrophes. They are usually poor, live under dismal conditions, and encompass 70—90% women and children. In addition to the demographic, political, cultural and societal consequences of this global ethnic displacement, serious problems arise regarding infectious diseases.[6] In the short term their spreading typically involves infections associated with poor hygiene, poor access to safe water, promiscuity or overpopulated living quarters. Diarrheal diseases, upper respiratory disease, hepatitis and sexually transmitted infections, are the main infectious consequences of this acute situation. The incubation periods of many of these infectious diseases are longer than modern travel times, rendering old fashioned quarantine measures obsolete. In a longer timescale, more hidden, chronic diseases also have to be considered because they create new public health conditions, which require a reorganization of the health care system in order to control them. Examples include multidrug resistant tuberculosis, hepatitis B, hepatitis C and hepatoma, papilloma virus and cervical cancer, HIV and other lentivirus.

The food market

The food market has also followed the globalization process, and — as demonstrated by bovine spongiform encephalopathy and its health and political consequences — has become impossible to control. This is also true for less dramatic food-borne diseases: thus, it is estimated that in the US, 76 million cases of food-borne disease occur each year, of which the known conventional and well known pathogens represent only 14 million (20%) — about 20 bacterial species, five parasites and four groups of viral agents.[7] This network of mass cultivation of food products, of conditioning, mixing, importing and exporting food products, not to speak about massive meal preparations for schools, cafeterias etc, has become so entangled and complex that its control by usual public health measures is beyond our capability.

Bioterrorism

Six billion humans have progressively conquered our planet and have thereby created new living conditions that are conducive to the widespread development of old and new infectious diseases; this historical movement, known since the Renaissance and recently amplified, has abolished ecological niches of pathogens and put them into contact with new, susceptible populations. This process is still under way and further 'encounters' of locally adapted, or even hidden, new pathogens by susceptible individuals can be foreseen. This risk will be difficult to manage in a world of little concern for potential dangers. This undesired globalized risk due to lack of foresight is presently further aggravated by another potentially devastating phenomenon, i.e. voluntary contamination or bioterrorism. Many leading personalities in the world of microbiology, among them the Nobel Prize winner Joshua Lederberg, have warned for many years that microorganisms could be used as 'the poor nation's atomic bomb'. Today the list encompasses five major pathogens. Anthrax,[8,9] botulism,[10] tularemia, plague, smallpox,[11] and genetically modified infectious agents. All these organisms have received adequate coverage by the medical and lay press, and will therefore not be discussed. A few general comments are nevertheless in order: the recent bioterrorism threats have revealed that bioterrorist strategies have been developed in hiding for many years and 17 countries have acknowledged that they have had an offensive biowarfare program.

Several attempts to use bioterrorist weapons actively have fortunately failed on a large scale. This is certainly not reassuring. Although the manufacturing of lethal bioweapons requires access to advanced technology, even their limited use in a well concerted strategy can have psychological, societal and political impacts almost as important in their paralyzing effect as the eradication of a whole population segment, as demonstrated by the recent anthrax threat in the US and in other countries. Moreover, local decontamination will entail solving almost insurmountable problems, as shown by a UK report after World War II: 36 years later, in a small island off the Scottish coast which was used for anthrax exposure testing, the ground still contained anthrax spores and required 280 tons of formaldehyde for decontamination.

Examples of emergent and re-emergent infectious diseases

The list of new organisms or re-emergent organisms is, by definition, incomplete, constantly changing and operational.[12,13] Table 1 is not intended to give a complete overview, but rather to show the immense diversity of the most important emergent pathogens. Such a list would not be complete without mentioning another type of emergent epidemic, maybe the most important one, also caused by our

Table 1 Examples of emerging and reemerging infectious diseases. (Incomplete) (modified from Gushulak[6]).

Infectious agent	Clinical outcome
Prion agent and BSE	Var. Creutzfeld Jakob disease
Viruses	
Hantavirus	Chronic renal failure
Hepatitis B	Chronic hepatitis, hepatoma
Hepatitis C	Chronic hepatitis, hepatoma
HIV	AIDS
HTLV	Lymphoma
Papilloma	Cervical carcinoma
Dengue	Extension of risk area
West Nile Fever	Encephalitis with ↑ mortality: US, Israel, etc.
Bacteria	
Helicobacter pylori	Peptic ulcer, gastric carcinoma
Mycobacterium tuberculosis	Reactivation tuberculosis
Multidrug resistance: Salmonella spp, Shigella spp, Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis	Increased morbidity and mortality
Parasites	
Trypanosoma cruzi	Chronic Chagas disease
Plasmodium falciparum	Extension of malaria

own mismanagement — the new epidemic of multidrug resistance.

The discovery and development of antimicrobials, only 60 years ago, has indeed added a formidable pressure on the microbial population in contact with the human species. However microbial adaptation has been not only multifaceted, but also fast when compared to the previous evolution of life. So far, resistance to antimicrobials has developed among any pathogen (bacteria, viruses, parasites) exposed to any new antiinfective agents.

The mechanisms of bacterial resistance are essentially of two genetic types:[14,15] mutation, and various genetic exchange systems such as transduction and conjugation. If these biological mechanisms create the genetic blueprint for new resistance patterns, it is their proliferation under selective pressure which creates the conditions for new epidemics (hospitals, agriculture, ambulatory care facilities). A recent study, sponsored by the European Community banning a vancomycin analogue (aparmycin) from animal feed and resulting in a decreased prevalence of vancomycin resistant enterococci, is a case in point to show us where future strategies should go, if we do not want to find ourselves at the end of the antibiotic era.[16]

New opportunities and strategies

In this globalized world, the human species is again endangered by infectious diseases and will have to use all its creative strength to find new solutions: this new world now requires new scientific approaches. Scientific research has evolved in recent times more towards understanding these phenomena at the micro- and even at the nanolevel, rather than in their global expression of complexity. Without belittling the important discoveries made in epidemiology and environmental research, we must appreciate that it is mostly at the small scale level that the impetus of science has its major impact today. In the following, new developments at the micro- and nanolevel of life sciences will be described, which will hopefully help to solve some of the major challenges to mankind previously described. A few important developments — methodological, scientific, technical — will be described which will in all probability deeply influence our understanding of infectious diseases.

Quorum sensing

It is generally accepted that within a colony or an infectious process, all bacteria are identical and represent a clone originating from an original blueprint. Important new scientific information gathered over the last few years has shown, however, that a given bacterial population is heterogenous, and that the individual behaviour of each cell is determined by factors linked with the population density: soluble compounds are liberated by each cell into its surroundings, affecting through a receptor-second-messenger mechanism, the neighbouring cells;[17] this is an 'effect at a distance' akin to the pheromone action in insects. The mechanisms underlying this phenomenon have been elucidated in many species, including *Staphylococcus aureus*: the pheromone here is an eight aminoacid peptide, and the process is population density dependent. At the end of an exponential growth phase, this cell-to-cell interaction mechanism causes down-regulation of cell surface components (unnecessary for survival at this stage) and upregulation of secretion factors and toxins.[18] This expanding new universe of interbacterial communication offers totally new avenues for useful applications in biotechnology, ecology and human diseases. Substances inhibiting cell-to-cell communication could well avoid the establishment of bacterial nidation and represent a new generation of antimicrobials which are less prone to the emergence of resistance.

Genomics

The whole bacterial genome resides in a molecule 1 femtogram in weight. Whereas until recently, the isolation or/and characterization of a single gene was a PhD performance, new technologies have driven this field to allow rapid high throughput screening of whole bacterial genomes. By 2001, 37 microbial genome sequences had been completed, and 142 were in progress worldwide.[19] The recent development of robotics to achieve high spotting densities of DNA on glass slides allows the construction of microarrays containing up to 50,000 genes on a single microscopic slide. This sequencing technique helps to accumulate important data that could usefully answer many important questions regarding human pathogens: bacterial evolution, identification of potential virulence genes, analysis of epidemics and rapid diagnostic methods in clinical microbiology, are but a few among the most important ones.

Microbial gene expression profiling

Microbial gene expression profiling has rapidly taken the lead in this field and is superseding simple genome sequencing: assessment of transcription with cDNA microarrays provides a dynamic picture of microbial or host tissue behaviour 'in real life' i.e., during the infectious process.[20] Gene expression profiling allows observation of 'life in the city' under the most diverse conditions.[21] The technical problems of unstable mRNA have been largely solved, and enormous quantities of data at various time points can be analyzed by bioinformatics tools or expressed visually. Bacterial targets essential for survival can thus be identified, allowing the screening of new compounds active on highly conserved targets in various species — a condition necessary for broad spectrum antimicrobials — or inversely hitting specific targets — a condition necessary for selective therapy. Bioinformatics tools and high throughput screening are indispensable technologies to master these new strategies.

Such genome expression analysis will help in the search for new antibiotics and will supersede the usual, conventional and time-honoured approach of whole cell antimicrobial screening; although this methodology has been historically successful and reproducible, it is rather insensitive, empirical, and has led to the limited discovery of natural compounds with narrow targets: the cell wall, protein synthesis and DNA replication. The novel approach based on genome expression, very sensitive and efficient, detects new potential action sites and favours a rational drug design.[22] Problems to be solved will include penetration issues, identification of processes independent of gene expression and — as always — the long itinerary of research from the bench to the bedside.

Data handling and simulation systems

The data which accumulate in microbiology and in life sciences no longer allow all new hypotheses and experimental conditions to be put to the test. Virtual experimentation has therefore become part of laboratory exploration, as shown recently with the publication of an artificial cell — the e-cell.[23] This model has 102 protein encoding genes and 22 RNA encoding genes, and consists in 495 reaction rules. When simulation starts, all reactions are started in parallel and the genomic expressions are monitored using a genemap window. This allows artificial testing of various conditions, thereby allowing concentration on crucial real experiments.

Combinatorial chemistry

Combinatorial chemistry has also evolved as an efficient tool in the screening for new antiinfectives, in association with other experimental procedures. The strategies followed are the systematic search for novel targets, the improvement of compounds inhibiting resistance enzymes, or the modification of known, useful antibiotics. Vancomycin is an interesting case in point. Derivatives of vancomycin — an antibacterial which has increased activity as a dimer — can be reconstructed with various new building blocks in the presence of its usual

Table 2 Nanosciences and nanotechnology.

Examples
Nanospheres (Fullerenes), nanotubes, nanostructures
Nanocapsules (with receptors), nanorobots, nanomotors
Nanosensors (intracellular)
Self replicating biowatch
Applications
Sensors: pressure, olfactory, chemical
Nanobots: clot lysis, arterial repair, tumour destruction
Self assembly: toxicology, environment

substrates, and its potential increase in antibiotic action, tested first in computer models and thereafter in an in vitro system.

Nanotechnology and nanobiology

In recent years, remarkable progress has been achieved at an ever lower level of the life scale — at the level of the nanometer. Search for drug discovery and delivery is moving smaller;[23,24] drug targeting against tumour vessels for instance has become now a reality,[25] and many new biologically active nanostructures are being developed: 'Macrodoctors, come meet the nanodoctors' is soon to become a reality (Table 2).[26]

Vaccinology

Modern vaccinology has also made spectacular progress in recent years by the use of the most modern technologies. The list regarding the production of active immunization systems is indeed impressive.[27] The eradication of many diseases around the world has now become a realistic goal. Long term consequences of chronic diseases, such as hepatitis B induced hepatoma, have been clearly shown to be drastically reduced among children in Taiwan.[28] New vaccine strategies are being explored, such as the use of conjugated vaccines, recombinant proteins, pseudovirions and DNA vaccines. Delivery systems are also improving with the exploration and implementation of transdermal applications, microencapsulation and plant expression of antigens. It is hoped that research in this field will soon help to control, at affordable prices, diseases such as malaria, HIV, and *M. tuberculosis*. A list of the immunization procedures available today or in a near future is given in Table 3.

An attempt at integration — conclusions

If yesterday these two worlds, the microbial world and human civilization, were limited in their contact by environmental conditions determining ecological niches, modern life has dramatically changed this ordered relationship. We are the witnesses and also the pilots and victims of a new, disrupted system, where the old rules of limited mutual interaction are no longer valid. Frontiers are abolished; free circulation of man and products is the rule; human immigration into cities leads to new microbial concentrations; massive influence of civilization on the environment reshuffles epidemiologic conditions — infectious diseases in particular and health in general have also become globalized (Figure 1).

It is time, therefore, to consider new solutions at the global level — at country, continent, and planetary levels. Infectious diseases in modern times can only be comprehended as a science with a new approach acknowledging the environment as

Table 3 The status of vaccines against human pathogens (modified from Ada[27]).

Bacteria	Viruses	Parasites
Bacillus anthracis	Adenovirus	Leishmania (phase 3)
Bordetella pertussis	Hepatitis A	Coccidioides (phase 2)
Borrelia burgdorferi	Hepatitis B	
Clostridium tetani	Influenza A, B (phase 3)	
Corynebacterium diphtheriae	Japanese encephalitis	
Coxiella burnetii	Measles	
Mycobacterium leprae (phase 2)	Polio	
Mycobacterium tuberculosis	Rabies	
Neisseria meningitidis	Rubella	
Salmonella typhi	Vaccinia	
Streptococcus pneumoniae	Varicella-Zoster	
Vibrio cholerae	Yellow fever	

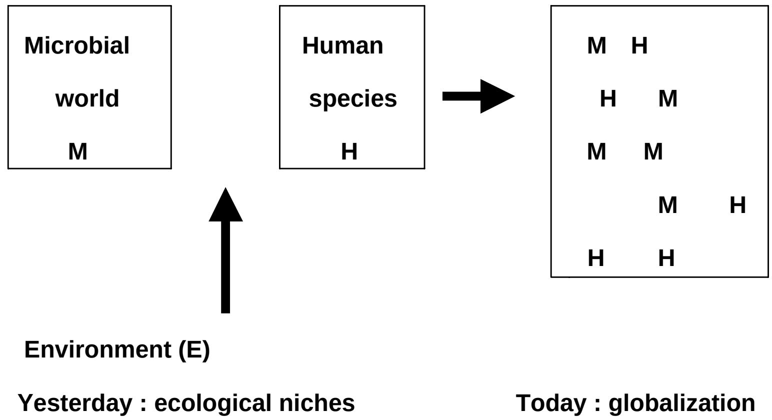

Figure 1 An attempt at integration: conclusions.

one of the important players in the field; hospital and public health, geographical, societal and political strategies have to be included in eradication strategies. The modern infectious diseases specialist has therefore to be a socially conscious, responsible person, more so than any other specialist in medicine except, maybe, the psychiatrist. Areas of general interest and importance, and in which rapid progress should be made include the following:

- Sustainability, in order to prevent the irreversible transgression of critical thresholds (ocean belt conveyors, ice shield, ozone layer, rain forests) which could alter dramatically our living conditions
- Epidemiology, with an expansion into new fields driving this science, such as economic, social, behavioural contexts
- Collective action: setting up and implementing general rules and regulations for migrants, refugees, travel, antibiotic misuse, food market and network; in addition, all these changing conditions require the development of a vast early global warming system, akin to the high performance computer networks — the grids — set up by physicists and mathematicians
- Public health practices have to be rapidly and dramatically improved and collective action at the population level is rapidly required. In particular, the problem of water access should be put on national and international agendas and prioritized within the next few years, if we want to avoid a major political crisis or a mere economic solution to the problem
- Control of the human and non-human usage of antiinfectives will become a necessity, and it is high time to reinforce the established rules and regulations, if we do not want the era of antibiotics to come to a rapid end.

Such approaches are highly complex if considered in their globality — they need to be redefined in terms of either accessible or affordable subprojects. They also entail, as mentioned before, the use or development of new, powerful scientific tools. So far, we have relied mostly on conventional methods, logistics and tools, but new domains in science are developing rapidly which we may take advantage of. The previously mentioned challenges can be approached in a more visionary way with new scientific tools, which have evolved into new opportunities. All these new domains of science and technology are not specific to infectious diseases, but are used extensively in many other fields of science, engineering, economics, and are reciprocally fuelled by these domains. They represent a unique chance to solve some of the most important problems of mankind.

In summary, the juxtaposition of old challenges and new opportunities in the infectious disease world of the 21st century unveils major, potentially dramatic problems, and simultaneously suggests new approaches based on new domains of science and technology to solve or mitigate them. It is an exciting time, since old challenges can be met by new opportunities. This will only be possible if scientists themselves become socially cognizant and ready to make society's needs a priority of their research. Nowotny and Gibbons[29] have described this commitment of scientists as 'socially robust science'. This clear commitment to societal needs is a necessary condition if we want to provide decent living conditions for the next generations.

In addition, the social responsibility of science has also to define how the individual's rights are to be respected. The events of September 2001, the many wars worldwide, the threat of bioterrorism, all lead to stronger policing systems, instead of democratic governments: the security of the world has certainly to be enhanced, but not at the price of reducing the individual's.

Finally, besides modern science and technology organized into a socially robust system to meet the challenges of the 21st century, two important issues have to be dealt with urgently. Education, particularly of women, and human rights — as fought for by the late Jonathan Mann — are indispensable for the development of a better world, in which the challenges of infectious diseases and health are balanced by equal opportunities for all.

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