Multifactorial Changes in Human Behavior, Environment, Climate Vectors and Zoonoses Enhance the Emergence and Reemergence of Human Microbial Diseases

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The human population of the world, in all its continents, has reached the level of 6 billion inhabitants. The constant growth of the population was bound to increase the need for food and dwellings, thus expanding the contact of humans with wild life and new pathogens in the environment – like the dwindling rain forests. In addition to the constant migration of humans from the deprived to the affluent continents, the travel of tourists from developed to developing countries and the increased transport of commercial products have led to an ongoing spread of insects, wild animals and plants around the world. In similar ways, people are invading territories where unknown bacteria and viruses are transmitted by insects from infected animals, which are the reservoirs. Transmitted by bats, viruses of wild birds and domestic and wild animals have the opportunity to infect humans with viruses or pathogenic protozoa.

These new pathogenic microbial agents are termed "emerging" disease-causing agents and are, or may be, the cause of new human epidemics. The importance of research on these new emerging agents prompted the Center of Disease Control, of the U.S. Department of Health and Human Services, in 1995, to launch a new journal entitled "Emerging Infectious Diseases" in printed and Internet forms [1].

The emerging microbial agents join the reemerging pathogenic microbial agents that became resistant to antibacterial drugs (e.g., mutations in the tuburcule bacillus), leading to drug resistance or mutations in virus genes, or new gene assortments that lead to pathogenicity of influenza virus (e.g., chicken influenza virus H5N1). During the latter half of the twentieth century successful advances in antimicrobial drugs and vaccines led to a marked increase in human life expectancy in the developed countries.

The twenty first century, however, needs new tactics for combating the emerging and reemerging microbial diseases. The importance of this subject is reflected in an article in this issue of *IMAJ* by Berns and Rager [2], who express their concern that inadequate public health programs around the world will not be able to contain emerging microbial diseases.

Microbial diseases and human antimicrobial defenses

From epidemiological studies on bacterial and viral epidemics in wild life and in humans, it was noted that different microbial pathogens differ in their morbidity and mortality rates in different human age groups. Pandemics caused by influenza viruses during the 1960s affected mostly young children and the elderly, while only some adults showed disease symptoms. Yet, the influenza pandemic of 1918 (Spanish flu) killed millions of young adults. Even in the Ebola virus epidemics, which caused a very high mortality of infected patients, only a few diseased individuals recuperated. The reason for the different responses to microbial infections in different human populations around the world lies in the genetics of the immune system that protects each individual from microbial diseases. Essentially, the infected person's immune system is composed of defenses at four levels:

- *The immediate cellular defense*, which operates during the first 24 hours after a virus infection when the infected cells attempt to degrade the infecting microbial agent by "switching on" the controlled cell death (apoptosis) and synthesizing interferons. If these processes fail to deter the invading pathogen the next stage begins.
- *The immediate early defense* (12–48 hours post-infection) becomes operational. The dendritic Langerhans cell system at the site of primary infection adsorbs the pathogen and degrades the microbial proteins. The dendritic cells migrate to the regional lymph nodes and induce the antimicrobial cytotoxic T cells to recognize infected cells. These cyctotoxic T cells migrate to the site of infection and attack and destroy the infected cells.
- *The early control system*, which is also induced in the patient, includes the acute phase response (e.g., induction of fever) [2].

- *The late immune response phase* (4–14 days), which includes the activation of the humoral immune system cells that produce antimicrobial antibodies [manuscript in preparation]. In this final stage, removal of the residual pathogens enables recovery from the microbial infection and repair of damaged tissues.

All the molecular processes of the human antimicrobial defenses are modulated by chemokines and cytokines, but their utilization in the enhancement of the immune systems of patients with a microbial disease had not yet been fully exploited.

Microbial diseases and the genetics of human resistance

Another parameter of the ability of a patient to resist a microbial pathogen (such as parasitic protozoa and micro-organisms) is the induction of cytotoxic T cells in the infected individual. This means the ability of the DC/LC to present a nonapeptide of 10 amino acid (derived from the pathogen protein) by HLA class I haplotype (one of the known haplotypes A, B, C and E). The T cell receptors that interact with the HLA class I molecules on the surface of the DC/LC confer the recognition of the microbe-infected cells by the CTL.

In a case-control study of malaria in West Africa conducted by Hill et al. [3,4], children with HLA class I B53 and an HLA class II haplotype (DR1*1302-DRB1*0501) were independently associated with protection from severe malaria. These data support the hypotheses that the extraordinary polymorphism of major histocompatibility complex genes has evolved primarily through natural selection by infectious pathogens. Europeans who entered the malaria endemic area did not have the HLA class I and II haplotypes that protect against malaria. Singh et al. [5] summarized the role of specific HLA class I and class II haplotypes in sensitivity or resistance to pathogenic bacterial, viral and parasitic pathogens.

Emerging zoonoses

The reports by Hill et al. [3,4] revealed that the endogenous population in malaria-endemic West Africa had evolved to express HLA class I and class II haplotypes, which protected them against severe malaria. This is due to a single nonapeptide that was derived by proteolysis of a malaria protein in the antigen-presenting cells. The malaria parasite, as well as many encephalitic viruses, are transmitted by mosquitoes. But it is the changing weather due to global warming that influences the distribution of the mosquito vectors which spread microbial pathogens to sensitive human populations. Epstein [6] indicated that due to global warming, microbial diseases and their carriers had reached higher mountain elevations whose inhabitants were exposed to malaria (the highlands in Ethiopia, Rwanda, Uganda and Zimbabwe), Dengue fever (Costa Rica and Mexico), and yellow fever (eastern Andes Mountains and northern highlands of India).

Epstein [6] also offered a possible explanation for how the warming trend and sequential weather extremes helped the West Nile virus to establish itself in the New York City area in 1999. Whether the virus entered the USA via mosquitoes, boats, migrating birds or people is not known. But once the virus arrived in New York, interactions between mosquitoes and birds amplified its proliferation. The 1999 dry spring and summer had killed predators of mosquitoes and led to the congregation of birds at dwindling water sources. A heat wave in July 1999 followed by drenching rains in August and September led to the transmission of WNV to the human population, causing severe disease and mortality in older people.

In Israel, WNV was isolated from a patient during the 1953 epidemic by Bernkopf and colleagues [7] in the virus laboratory of the Institute of Microbiology of the Hebrew University Medical School in Jerusalem. The current WNV epidemic in Israel is a reminder that the virus is endemic in our country.

Can West Nile outbreaks be controlled? This question is the subject of a review in the October issue of *IMAJ* [8], by Lustig and collaborators from the Department of Infectious Diseases, Israel Institute of Biological Research. This question is relevant since from the beginning of the WNV epidemic in Israel until 18 October of this year, 27 patients had died from WNV infections and 396 people with WNV symptoms were hospitalized. This indicates that many more people were infected by WNV even though they did not show symptoms of the infection. The WNV epidemic is self-limiting when the climate changes and the mosquitoes disappear due to cold weather. Lustig et al. [8] describe the properties of a laboratory-attenuated WNV, which lacks pathogenicity to laboratory animals and produces protective neutralizing antibodies in immunized mice and geese. The authors suggested the possible use of the attenuated WNV as a vaccine candidate for humans.

Recently, the National Institute of Allergy and Infectious Diseases at the National Institutes of Health in Bethesda, USA, reported in a fact sheet entitled "NIAID Research on West Nile an Related Viruses" that three R&D groups in the U.S. are involved in developing new live vaccines against WNV [9]. These vaccines utilize the apathogenic Yellow Fever virus as a carrier of the WNV genes. Dr. Robert Sidwell, the inventor of the antiviral drug ribavirin is screening chemical compounds for possible activity against WNV. Yet, during recent years, effective antiviral DNA vaccines had been developed in many laboratories against viruses, bacteria and pathogenic protozoa. It was recently announced that a DNA vaccine was approved for testing in humans. It is hoped that new antivirals and effective

DC = dentritic cells
LC = Langerhans cells
CTL = cytotoxic T cells

WNV = West Nile virus

vaccines will become available for immunization of people in WNV endemic regions.

The scope of emerging infectious diseases and the role of genomic research

The emerging infectious diseases of wildlife are a threat not only to human health but also to wild animals [10]. Daszak et al. [10] indicated that emerging infectious diseases of free-living wild animals can be classified as the transfer of these diseases from domestic animals to wildlife populations, and from wildlife to humans. An example of an emerging infectious disease of humans transferred to wildlife is the measles virus infection of Rwanda's mountain gorillas by human tourists [11].

The list of emerging infectious diseases is quite extensive [2,10] and includes new viruses and bacteria as well as known bacteria, such as those responsible for nosocomial infections in hospitals [12] (e.g., *Neisseria meningitidis* serogroup B, the cause of septicemia and meningococcal infection). The genome of *N. meningitidis* serogroup B was recently deciphered [13], and the selection of bacterial vaccine candidates was based on genomic and proteomic information [14].

It is hoped that in the near future new vaccines based on genomic and proteomic analysis of emerging infectious diseases will be developed to protect the human population against new and old microbial pathogens. Computation molecular biology of DNA genomes and proteins of microbial pathogens will allow the new synthetic antimicrobial agents to treat microbial infections in humans. Understanding of the HLA class I and II genetics of human populations, coupled with the molecular analyses of an emerging pathogen, will eventually allow the rapid production of synthetic DNA and peptide vaccines for human use in emergency situations.

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Try to learn something about everything and everything about something.

Thomas H. Huxley, English biologist (1825–95)

Capsule

Line of defense

The epithelial monolayer of the small intestine needs to be well protected against bacterial colonization and invasion. Specialized Paneth cells, located at the base of the small intestinal crypts of Lieberkuhn, contain granules of preformed microbicidal polypeptides known as alfa-defensins or cryptdins. The Paneth cell defensins are known to be secreted in response to cholinergic stimulation; however Ayabe et al. discovered that bacteria could stimulate Paneth cells directly to secrete these weapons. When they isolated crypt cells from mouse gut and incubated them with *Salmonella typhimurium*, *Escherichia coli*, or *Staphylococcus aureus*, up to 90% of the bacteria were killed, but only a third as many of cryptdin-negative mutants were used. They found that a wide variety of bacterial antigens stimulated Paneth cells to degranulate, and they concluded that common pattern recognition events triggered the exocytosis.

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