

## Original Contribution

# Pathocenosis: A Holistic Approach to Disease Ecology

Jean-Paul Gonzalez,<sup>1,2,3</sup> Micheline Guiserix,<sup>4</sup> Frank Sauvage,<sup>4</sup> Jean-Sébastien Guitton,<sup>5</sup> Pierre Vidal,<sup>6</sup> Nargès Bahi-Jaber,<sup>7</sup> Hechmi Louzir,<sup>7</sup> and Dominique Pontier<sup>4</sup>

<sup>1</sup>International Centre for Scientific Researches, Franceville (CIRMF), BP 2105 Libreville, Gabon

<sup>2</sup>French Ministry of Foreign and European Affairs, Paris, France

<sup>3</sup>Department of Health and Societies, Institut de Recherche pour le Développement, Marseille, France

<sup>4</sup>UMR-CNRS 5558, Université de Lyon, Université Lyon 1, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France

<sup>5</sup>Office National de la Chasse et de la Faune Sauvage, Direction des Études et de la Recherche, 39 Bd Albert Einstein, CS 42355, 44323 Nantes Cedex 3, France

<sup>6</sup>Department of Anthropology, Paris X University and French Ministry of Foreign Affairs, 11340 Roquefeuil, France

<sup>7</sup>Laboratoire d'Immunopathologie, Vaccinologie et Génétique Moléculaire, Institut Pasteur de Tunis, 13 Place Pasteur, 1002 Tunis-Belvédère, Tunisia

**Abstract:** The History of medicine describes the emergence and recognition of infectious diseases, and human attempts to stem them. It also throws light on the role of changing environmental conditions on disease emergence/re-emergence, establishment and, sometimes, disappearance. However, the dynamics of infectious diseases is also influenced by the relationships between the community of interacting infectious agents present at a given time in a given territory, a concept that Mirko Grmek, an historian of medicine, conceptualized with the word “pathocenosis”. The spatial and temporal evolution of diseases, when observed at the appropriate scales, illustrates how a change in the pathocenosis, whether of “natural” or anthropic origin, can lead to the emergence and spread of diseases.

**Keywords:** pathocenosis, emergence, infectious diseases

## INTRODUCTION

The history of medicine gives the epidemiology of infectious diseases a unique perspective in time and space, highlighting possible relationships between different diseases occurring in particular economic and social contexts.

In 1933, Charles Nicolle proposed a dynamic concept of the “birth, life and death of infectious diseases” to highlight the continuity and dynamics of what we could call the pathogenic domain of a given host population, i.e., the disease combinations observed at a given time (Nicolle,

1933). This approach focuses on the processes of disease development and succession at the scale of the host population. Charles Nicolle (1919 in Blanc and Baltazard, 1944) also proposed the pioneering concept of “asymptomatic infection,” crucial for understanding the sudden appearance (i.e., emergence) of certain diseases through clinical signs in particular circumstances.

In 1969, Mirko Grmek proposed considering diseases of a given host population as a whole, including their historical and geographic dimensions. By analogy with “biocenosis,” which is the ecological concept of all living organisms that coexist and interact within a defined territory, Grmek defined pathocenosis as follows: “By pathocenosis, I mean the qualitatively and quantitatively defined group of

pathological states present in a given population at a given time. The frequency and the distribution of each disease depend not only on endogenous—infectivity, virulence, route of infection, vector—and ecological factors—climate, urbanization, promiscuity—but also on frequency and distribution of all the other diseases within the same population” (Grmek, 1969). Thus, for the first time in the history of medicine—beyond a nosological framework that encloses diseases in a frozen disciplinary framework (e.g., respiratory diseases, arboviral diseases, sexually transmitted diseases)—Grmek offered a temporal and spatial approach to understand the dynamics of infectious diseases and their interdependency. Grmek (1969, 1997) saw the health state of a population as a complex dynamic phenomenon leading to a wide range of epidemiological patterns subject to environmental and human factors. Based on this concept of “pathocenosis,” Grmek examined the historical progression of diseases across Europe during the past two millennia: over time, plague succeeded leprosy and was successively followed by syphilis, smallpox, cholera, tuberculosis, and, most recently, the acquired immune deficiency syndrome (AIDS). Even if such a succession can be coincidental, or if appearance and disappearance of successive diseases may have the same causes, these observations raise the question of interactive causalities.

Following Mirko Grmek, we propose to revisit some changes in pathocenosis in the light of the complex and dynamic processes in which the infectious agents potentially interact, keeping in mind the importance of the “asymptomatic infections” highlighted by Charles Nicolle.

## CONCEPT OF PATHOCENOSIS IN THE LIGHT OF THE HISTORY OF PLAGUE IN EUROPE

---

Revisiting disease history in the light of the pathocenotic concept, i.e., taking account not only of the environmental and social contexts but also of the presence of other diseases or infections in the host population, provides new explanations for observed sequences of events. The history of plague pandemics illustrates several aspects of disease interdependency, not only through the direct effects of the illness but also through the legacy of plague on the host population several centuries later (certain precautions must of course be taken, as medical knowledge was poor and unreliable at the time of the epidemics).

Historically, the Black Death followed on the heels of the peak in endemic leprosy, situated between the 12th and 14th

centuries. The massive human population declines due to plague epidemics (estimated at about 40% during the Black Death of 1347–1352 and 20% during the Great Plague of 1665–1666), from which Europe recovered only four centuries later, may be one cause of leprosy’s decline. The social consequences of the Plague affected the fundamental modes of transmission, as well as the distribution, of other pathogens associated with human population density (Weiss and McMichael, 2004). Thus, the Black Death probably induced strong competition for contemporary circulating pathogens, such as the smallpox and measles viruses, which are likely to have provoked outbreaks before the arrival of the bacterium *Yersinia pestis* and were only able to reemerge in the 18th century (Barquet and Domingo, 1997; Hopkins, 2002) once the Plague had vanished from Europe. The European Plague (1345–1750) also appears to have exerted major genetic selective pressure, maybe explaining the high frequency of the CCR5- $\Delta$ 32 deletion (10%), a protective allele, in the European population (Galvani and Slatkin, 2003; Duncan et al., 2005). This selection would constitute a major legacy of the Black Death and its resurgences, modulating the current pathocenosis by protecting against AIDS, for example. Finally, plague is a typical example of the strong interaction between human and animal pathocenoses. Indeed, human plague outbreaks interact with pathogens of the black rat, *Rattus rattus*, the carrier of *Y. pestis*. Serious plague outbreaks are usually preceded by highly lethal disease outbreaks in reservoir rodents, from plague or other diseases, which favor transmission of infected fleas to humans (Keeling and Gilligan, 2000; Duplantier et al., 2005; Lowell et al., 2009).

## DEFINING INTERACTIONS BETWEEN DISEASES AND INFECTIOUS AGENTS

---

Coinfection by more than one pathogen seems to be more common than infection by a single pathogen (Cox, 2001) and appears to affect the immune response to these agents (Graham et al., 2007). Cellular immune effectors (e.g., T helper 1, T helper 2, T helper 17, and cytokines) show complex mutual regulation, and this may affect the immune response to a second infectious agent. Witness the deleterious impact of nematode infestation on host immunity to infectious diseases such as malaria (Druilhe et al., 2005), hepatitis B and C (Kamal and Khalifa, 2006; Edwards et al., 2005) and AIDS, and even on the effectiveness of some vaccines (Su et al., 2006). Direct interactions between parasites have also been documented.

One example is hepatitis Delta virus, which cannot synthesize its own envelope protein and is thus dependent on coinfection by hepatitis B virus (Petney and Andrews, 1998). An “endopathocenosis” can exist within the individual host. In the digestive tract, the commensal bacterium *Escherichia coli* can produce an enterotoxin in certain microenvironments (pH variations), thus weakening the intestinal epithelium and facilitating massive invasion by potentially enteropathogenic viruses, such as rotavirus, picornavirus, and noroviruses (Lorrot and Vasseur, 2007).

Several types of relationships between diseases have been identified since Grmek put forward his hypothesis in 1969:

### Antagonism

One disease hinders the spread of another. For example, significant anemia impedes thalassemia and plasmodial infection (Veenemans et al., 2008); latent infection of mice by herpes murine viruses confers resistance against *Y. pestis* (Barton et al., 2007) or confers a partially immunological protection against another antigenically related infectious agent, as observed in flaviviruses. Indeed, antibodies against dengue virus strongly protect against experimental yellow fever virus infection (Brandiss et al., 1986), suggesting that the reason yellow fever appears never to have occurred in Asia maybe because of widespread immunity to dengue among Asian populations living in endemic areas (Monath, 2007).

### Synergy

One disease facilitates the introduction or development of another disease, as illustrated by antibody-dependent enhancement (ADE). According to this hypothesis, two consecutive infections by different dengue serotypes could favor dengue hemorrhagic fever (Kliks et al., 1988, 1989). “Opportunistic” microorganisms take advantage of a weakened immune system that has been compromised by AIDS or other causes, such as malnutrition, antibiotic treatment, and cancer chemotherapy, eventually leading to the emergence of other dominant clinical pictures (e.g., cryptococcosis, pneumocystosis, toxoplasmosis, and Kaposi’s sarcoma).

### Independence

Two diseases have no influence on each other, and their spread within the population of a given territory is independent.

## PATHOCENOTIC IMBALANCE AND DISEASE EMERGENCE

---

The pathocenosis can be stable (“endemic” or in equilibrium) in a stable ecological situation where the density and behaviors of the different components are not subject to major changes. This equilibrium can be disturbed, however, leading to sharp variations in the frequencies of certain diseases and even to the emergence of new diseases in a particular population or territory. Thus, a succession of disturbances can lead to a dynamic sequence of pathocenoses, one health state giving way to a new one after a period of upheaval.

Such perturbations include the introduction of infectious agents and environmental changes of “natural” or human origin. For instance, Zinkernagel (2001) pointed out that better hygiene has shifted the average age of infection by certain pathogens; as a result, some diseases that are benign in childhood have become more frequent in adults, in whom they are generally more severe. The same phenomenon is observed following mass vaccination campaigns (e.g., measles). The arrival of a new infectious agent can disclose the existence of a previously silent or unnoticed agent through synergistic interaction. For example, coinfection by childhood viruses (Epstein-Barr virus [EBV], human herpesvirus type 6 [HHV6], or cytomegalovirus [CMV]) could be a prerequisite for visceral leishmania onset following infection by *Leishmania infantum* (Louzir and Dellagi, 1999). Conversely, the emergence of an infectious agent can lead to the demise of another; although the mechanisms are controversial, tuberculosis may have had a role in the decline in leprosy in Europe during the 17th and 18th centuries (Lietman et al., 1997; Donoghue et al., 2005). Likewise, in an antagonistic interaction, the disappearance of one disease can pave the way for the reemergence of another (see the above-mentioned assumed relationships between plague and smallpox or measles). Any change in the circulation of these interacting viruses would modify the conditions and frequency of infection by the others and, thus, the epidemiology of the diseases.

## PATHOCENOSIS: A NEW PARADIGM FOR HUMAN MEDICINE

---

Currently, the emergence of an infectious disease is usually addressed from a monodisciplinary (i.e., biomedical) point

of view in the search for a cause. Studies of disease dynamics in vertebrate populations must take into consideration interactions with other components of the biosystem and, more generally, the ecosystem (Pontier et al., 2009). Likewise, it is essential to consider diseases as being potentially dependent on each other and to take into account environmental factors capable of modulating disease dynamics. The concept of pathocenosis is particularly useful for understanding the current emergence of infectious diseases, as the underlying mechanisms include interactions of infectious agents both with one another and with the environment.

Given the complexity and diversity of possible situations, one must first identify the key elements needed to provide a framework for studying pathocenosis and its dynamics, and eventually predict and prevent disease emergence. This framework could include the studies of: 1) the mechanisms of disease emergence within an established pathocenosis; 2) a typology of conditions leading to disease emergence; and 3) the spatial and temporal scales at which the pathocenosis can be understood. Grmek (1969) already noted that detecting transitions from endemic to epidemic states faces major but surmountable difficulties, and requires accurate diagnosis of all sick individuals in a population during a given period. The obstacles vary with historical times, but they must be overcome and, in a contemporary analysis, this requisite can be largely fulfilled. The identified general mechanisms then can be used to define the conditions of the greatest disease emergence risk (Pontier et al., 2009). The main challenge in understanding the succession of pathocenoses is finally to determine the spatial scale at which the phenomena must be studied (e.g., at the level of the village or the continent). Two typical examples are the hemorrhagic fevers of South America, caused by arenaviruses, which cocirculate within their natural hosts (rodents), and seasonal influenza pandemic. Rodents are found throughout the continent, but the arenavirus remains confined to areas of a few hundred square kilometers, and outbreak studies will generally focus on individual villages. In contrast, the prevention of seasonal flu pandemics requires, obviously, a global approach.

While most examples and references given in this article refer to infectious diseases (due to viruses, bacteria, parasites, and fungi), the pathocenosis also encompasses chronic diseases (diabetes, cancer, allergies), degenerative diseases (systemic diseases, cardiovascular diseases), and other health disorders (mental illness, trauma). The

hygiene hypothesis is based on a similar approach, directly linking the increased frequency of atopy and allergy to the reduction in the incidence of several infections, especially during childhood (Bach, 2005). The pathocenosis, as an integrative concept, helps us to consider health status holistically and in all its complexity, where the monodisciplinary approach prevents us from grasping the full complexity of a phenomenon. Moreover, the clinical expression of a given infection can vary with the characteristics of both the pathogen (genetically dependent virulence and infectivity) and the host (age, gender, genotype, physiological state, other infections). A better understanding of the dynamics of infections and the importance of asymptomatic infections thus requires all this information to be taken into account.

## CONCLUSION

---

The principal lesson of the pathocenotic concept is that disease prevention requires a global, comprehensive, and integrated approach. This important idea has been left behind during almost 40 years since Grmek raised it in 1969, likely due to the lack of data and methods required to test it. However, the recent methodological advances in field and theoretical work have recently enabled us to highlight many solid examples of diseases interactions. These studies need to be continued, since they are the only way to evaluate the importance of infections' interactions in epidemic patterns and disease emergence, and thus confirm that pathocenosis is more than an elegant idea proposed by a philosopher of science. This question is of major importance because, in the latter case, this concept should permit a revisiting of our knowledge about infectious diseases in an original manner, for better comprehension and more efficient control and prevention.

## ACKNOWLEDGMENTS

---

Financial support has been provided by the French National Agency for Research (ANR SEST “*Pathocénoses et émergence des maladies transmissibles: un concept unificateur mis à l’épreuve sur des pathologies exemplaires*”). We thank our colleagues from the ANR Pathocenosis Team for productive discussions, namely Philippe Barbazan, Afif Bensalah, Koussay Dellagi, David Fouchet, Stéphane Marchandeu, and Marc Souris.

## OPEN ACCESS

This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

## REFERENCES

- Bach JF (2005) Six questions about the hygiene hypothesis. *Cellular Immunology* 233:58–161
- Barquet N, Domingo P (1997) Smallpox: the triumph over the most terrible of the ministers of death. *Annals of Internal Medicine* 127:635–642
- Barton ES, White DW, Cathelyn JS, Brett-McClellan KA, Engle M, Diamond MS, et al. (2007) Herpesvirus latency confers symbiotic protection from bacterial infection. *Nature* 447:326–330
- Blanc G, Baltazard M (1944) Étude de l'immunité dans les fièvres exanthématiques. Qualité de l'immunité "Réinfection inapparente." *Archives de l'Institut Pasteur du Maroc* 2:633–650
- Brandiss MW, Shlesinger JJ, Walsh EE, Briselli M (1986) Lethal 17D yellow fever encephalitis in mice. I. Passive protection monoclonal antibodies to the envelope proteins of 17D yellow fever and dengue 2 viruses. *Journal of General Virology* 67:229–234
- Cox FEG (2001) Concomitant infections, parasites and immune response. *Parasitology* 122:S23–S28
- Donoghue HD, Marcsik A, Matheson C, Vernon K, Nuorala E, Molto JE, et al. (2005) Co-infection of *Mycobacterium tuberculosis* and *Mycobacterium leprae* in human archaeological samples: a possible explanation for the historical decline of leprosy. *Proceedings of the Royal Society of London. Series B: Biological Sciences* 272:389–394
- Druilhe P, Tall A, Sokhna C (2005) Worms can worsen malaria: towards a new means to roll back malaria? *Trends in Parasitology* 21:359–362
- Duncan SR, Scott S, Duncan CJ (2005) Reappraisal of the historical selective pressures for the CCR5-Δ32 mutation. *Journal of Medical Genetics* 42:205–208
- Duplantier JM, Duchemin JB, Chanteau S, Carniel E (2005) From the recent lessons of the Malagasy foci towards a global understanding of the factors involved in plague reemergence. *Veterinary Research* 36:437–453
- Edwards M, Buchatska O, Ashton M, Montoya M, Bickle Q, Borrow P (2005) Reciprocal immunomodulation in a schistosome and hepatotropic virus coinfection model. *Journal of Immunology* 175:6275–6285
- Galvani AP, Slatkin M (2003) Evaluating plague and smallpox as historical selective pressures for the CCR5-Δ32 HIV-resistance allele. *Proceedings of the National Academy of Sciences of the United States of America* 100:15276–15279
- Graham AL, Cattadori IM, Lloyd-Smith JO, Ferrari MJ, Bjornstad ON (2007) Transmission consequences of coinfection: cytokines writ large? *Trends in Parasitology* 23:284–291
- Grmek MD (1969) Préliminaire d'une étude historique des maladies. *Annales ESC* 24:1437–1483
- Grmek MD (1997) *Histoire de la Pensée Médicale en Occident—Tome 2, De la Renaissance aux Lumières*, Paris: Le Seuil
- Hopkins DR (2002) *The Greatest Killer: Smallpox in History*, Chicago: University of Chicago Press
- Kamal SM, Khalifa KE (2006) Immune modulation by helminthic infections: worms and viral infections. *Parasite Immunology* 28:483–496
- Keeling MJ, Gilligan CA (2000) Metapopulation dynamics of bubonic plague. *Nature* 407:903–906
- Kliks SC, Nimmanitya S, Nisalak A, Burke DS (1988) Evidence that maternal dengue antibodies are important in the development of dengue hemorrhagic fever in infants. *American Journal of Tropical Medicine and Hygiene* 38:411–419
- Kliks SC, Nisalak A, Brandt WE, Wahl L, Burke DS (1989) Antibody-dependent enhancement of dengue virus growth in human monocytes as a risk factor for dengue hemorrhagic fever. *American Journal of Tropical Medicine and Hygiene* 40:444–451
- Lietman T, Porco T, Blower S (1997) Leprosy and tuberculosis: the epidemiological consequences of cross-immunity. *American Journal of Public Health* 87:1923–1927
- Lorrot M, Vasseur M (2007) Physiopathology of rotavirus diarrhea. *Journal de Pédiatrie et de Puériculture* 20:330–336
- Louzir H, Dellagi K (1999) Les leishmanioses: un modèle d'étude des interactions hôte-parasite; implications pour la maladie humaine. *Annales de l'Institut Pasteur* 10:67–68
- Lowell JL, Eisen RJ, Schotthoefer AM, Xiaocheng L, Monteneri JA, Tanda D, et al. (2009) Colorado animal-based plague surveillance systems: relationships between targeted animal species and prediction efficacy of areas at risk for humans. *Journal of Vector Ecology* 34:22–31
- Monath TP (2007) Dengue and yellow fever—challenges for the development and use of vaccines. *New England Journal of Medicine* 357:2222–2225
- Nicolle C (1933) *Leçons du Collège de France: Destin des maladies infectieuses*, Paris: Felix Alcan
- Petney TN, Andrews RH (1998) Multiparasite communities in animals and humans: frequency, structure and pathogenic significance. *International Journal of Parasitology* 28:377–393
- Pontier D, Guiserix M, Fouchet D, Sauvage F, Gonzalez JP (2009) Emergence of infectious diseases: when hidden pathogens break out. *Comptes Rendus Biologies* 332:539–547
- Su Z, Segura M, Stevenson MM (2006) Reduced protective efficacy of blood-stage malaria vaccine by concurrent nematode infection. *Infection and Immunity* 74:2138–2144
- Veenemans J, Andang'o PE, Mbugi EV, Kraaijenhagen RJ, Mwaniki DL, Mockenhaupt FP, et al. (2008) Alpha+-thalassemia protects against anemia associated with asymptomatic malaria: evidence from community-based surveys in Tanzania and Kenya. *Journal of Infectious Diseases* 198:401–408
- Weiss RA, McMichael AJ (2004) Social and environmental risk factors in the emergence of infectious diseases. *Nature Medicine* 10(12 Suppl):S70–S76
- Zinkernagel RM (2001) Maternal antibodies, childhood infections and autoimmune diseases. *New England Journal of Medicine* 345:1331–1335