Carlo Modonesi^{1,2,3}, Enrico Oddone⁴, Celestino Panizza^{3,5}, Marcello Imbriani⁴

The missing link between human ecology and public health: the case of cancer

- ¹ Cancer Registry and Environmental Epidemiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
- ² Department of Chemistry, Life Sciences and Environmental Sustainability, Università degli Studi di Parma, Parma, Italy
- ³ International Society of Doctors for the Environment (ISDE)
- ⁴ Department of Public Health, Experimental and Forensic Medicine, Occupational Medicine Unit, Università degli Studi di Pavia, Pavia, Italy
- ⁵ Service for Occupational Safety and Prevention, Azienda Sanitaria Locale (ASL), Brescia, Italy

ABSTRACT. The primary role played by the 'ecological context' in clarifying the causes and dynamics of human health and disease is the topic of this article. It emphasizes that the challenging incidence of cancer and other diseases can be charged primarily to the effects of the worldwide dominant economic model.

Human culture may act as a powerful force affecting the environment, biology and health of humans and other species. Human culture can be viewed as a special and extreme case of 'niche construction', where human-specific traits, technologies and beliefs act together.

The feedback between human activities and the environment can promote different trends in public health. This should provide the opportunity to rethink the consequences that our economic model produces both on the environment and on physical, mental and social health of our species.

Key words: human ecology, cancer, economic model, environment.

RIASSUNTO. Il ruolo di primo piano giocato dal contesto ecologico nella chiarificazione delle cause e delle dinamiche della salute umana e, per contro, degli stati di malattia è il focus di questo lavoro. La preoccupante incidenza del cancro e di altre patologie degenerative può essere attribuita in larga parte al modello economico dominante a livello globale. La cultura umana può agire come una forza potente, capace di influenzare negativamente l'ambiente di vita, la biologia e perfino lo stato di salute dell'uomo e di altre specie. La cultura umana può quindi essere vista come un caso estremo di niche construction, dove le caratteristiche biologiche, le tecnologie e le credenze umane agiscono insieme nella cosiddetta 'costruzione della nicchia ecologica' della nostra specie.

Il feedback tra attività umane e ambiente può promuovere trend di salute pubblica differenti. Ciò costituisce un'opportunità per guardare in modo diverso alle conseguenze che il nostro modello economico produce non solo a livello ambientale, ma anche sulla salute fisica, mentale e sociale della specie umana.

Parole chiave: ecologia umana, cancro, modello economico, ambiente

Introduction

This article is not aimed to produce new scientific data. It rather represents an effort to point out the primary role played by the 'ecological context' in exploring causes and dynamics of human health and disease.

Here the phrase 'ecological context' is referred not only to the physical and biological environment of individuals, but also to the social-economic condition that weights on their life. The term environment acquires a relevance involving aspects neglected by the conventional meaning.

The interest of naturalists in environmental health problems began in the '50s and did not overstep the boundaries of communicable diseases and their immediate implications for a long time. Early efforts to study infectious human pathologies and agents and biological vectors within an ecological framework were focused on the spread of malaria and its effects on the distribution of sickle-cell traits in poor regions of the world (1, 2). However, in 1960, the French physician and geographer Jacques M. May formalized the theoretical and empirical principles for exploring the close association between geographical environment and human disease. In his contribution, May defined disease – any disease – as 'a maladjustment to the environment' (3).

Nowadays, we know that also degenerative pathologies, like cancer or others, could be investigated by an effective ecological approach that tends to mitigate some substantial differences between communicable and noncommunicable diseases. In spite of the common belief that communicable diseases are always determined by a unique causing factor – the infectious agent – in the real world both typologies of diseases often share the traits of multifactorial and multilevel causation (4, 5).

Although these similarities are largely recognized, there has been a gap in managing communicable and non-communicable diseases in terms of primary prevention. The success in reducing infectious diseases was due to the implementation of systemic approaches in planning urban infrastructures (i.e. sewers), social policies, and later immunization programs. On the other hand, except for sporadic cases such as the taxation of cigarettes or the ban of trans fats from food industry in United States, similar approaches to prevent non-communicable diseases lack so far (6, 7).

The ecological determinants of disease

The feedback between human health and human exploitation of land – together with water and biological resources – was traditionally explored by anthropologists. Studies conducted among pre-contact or isolated nomadic modern populations of hunter-gatherers showed that where dietary resources were sufficient, malnutrition was rare. Moreover chronic diseases were relatively frequent and infectious disease rates varied mostly according to the human distribution on the land and to the geographic characteristics of the ecosystems (8).

In the last century, in most Western countries striking changes were recorded in disease patterns, i.e. the decrease of infectious diseases, malnutrition and, more recently, cardiovascular diseases (9). The populations of these countries became older and incidence rates of long-latency diseases grew as well. At the same time, these ageing societies were under the influence of new ecological factors linked to malignancies and to other degenerative pathologies (10). The reduction of old infectious diseases and the emergence of new degenerative ones were interpreted as unavoidable effects of the economic and technological development. This belief was formalized by the the so-called 'theory of epidemiological transition' (11). According to this theory, the declining mortality and the ageing population levels should have been determined by a linear shift in the causes of disease and death. Such a transition was perceived as a natural cost to pay because of the social advantages provided by the economic growth, being the GDP (Gross Domestic Product) a primary measure of the well-being of countries and people. This 'progressivist' thinking was developed for the first time in the Victorian Era but it still affects economists, politicians and scientists. The primary assumption is that the economic progress is real and objective, and is a universal value of the modern culture as well. According to this paradigm, the progress of the world is ineluctable, no matter that it is referred to humans or other living creatures (12). The theory of epidemiological transition was strongly criticized for the apparent relationships with the old 'progressivist' paradigm of natural sciences. It was argued that the appearance of *Homo sapiens* was a necessary step of animal evolution, one that still goes on through the modern 'economic evolution' (12).

Conversely, now we know that no deterministic and unavoidable force drives the history of the world and every evolutionary process is a product of multifactorial and contingent dynamics (13). Moreover, now we understand that health transitions are not linear and unidirectional changes, but they are complex processes showing counter-transitions with possible reemergence of diseases previously controlled (14, 15).

Many infectious diseases have an old record of cosmopolitan appearance, disappearance and recurrence. The new challenges introduced by the economic globalization processes are the scale and the speed by which people, products and infectious agents can travel across the planet. The number of potentially infectious contacts has exploded while trade and travel bring goods, organisms and

human beings closer than ever before. Nowadays the longest intercontinental flight is shorter than the incubation period of any known infectious pathogen. Moreover, the existing drugs have lost a substantial part of their effectiveness. This is especially due to improper practices that are responsible for the development of new forms of microbial adaptation which in turn have produced resistance to many antibiotics. The antibiotic resistance has become one of the most critical issues in the fight against communicable diseases (15).

Emerging and reemerging of communicable diseases

While non-communicable diseases are the most frequent causes of death in Americas, East Mediterranean, Europe, South-East Asia, and West Pacific, communicable diseases are coming back in a large part of the world. Even developed countries are not free from new infectious risks. Toxic shock syndrome, Chronic fatigue syndrome, Lassa fever, Ebola hemorrhagic fever, Hantavirus pulmonary syndrome, AIDS, sexually transmitted diseases, and other infectious diseases constitute a common and serious health threat (15).

Tubercolosis (TB) is a dramatic example of the challenging infectious risk in developed and developing countries. In 2003, around 9 million people became infected with TB worldwide, while more than 2 million died due to this recrudescence. Several causes were proposed to give an explanation to this alarming surprise. One was the suppression of the immune system of many people who got the infection, since TB is often the first sign that a person might have HIV. Other causes included overcrowding, poor nutrition, and inadequate health care, which are common among socially and/or environmentally marginalized people like migrants (15). Migrants from poor regions often represent a vulnerable fraction of the population, and the data on the Roma and TB in Central and Eastern Europe, as well as the current efforts by Governments and NGOs to address TB in these communities, confirm the relevance of the problem (16).

Not surprisingly, also in the American continent morbidity and mortality rates for HIV and TB are several times higher among migrants in the Northern border States of Mexico than in the United States as a whole. Likewise, more than 50% of TB cases in US are reported in the four States bordering Mexico. The latest entries in the list of the global recent epidemics are severe acute respiratory syndromes (SARS) and avian and swine flu. The SARS alarm of 2003 was the first serious warning of the potential health, social, economic, and security consequences of major disease outbreaks. H1N5 avian influenza has remained a regional threat, but H1N1 swine influenza produced a warning in 2009, when the outbreaks in Mexico and US spread worldwide in a short time (15).

Currently, the world is experiencing both the reemergence of old communicable diseases due to drug resistance and completely new communicable diseases due to ecologic and yet unclear causes. Drug resistance is a serious threat to global public health.

It would be possible to investigate the evolution of human disease-causing pathogens in space and time by crossing molecular analysis of infectious agents with analysis of interactions between population and environment. At population level, disease patterns could reflect the patterns of human-environment interplay: this is a way to conceive human health and disease dynamics usually ignored by most biomedical research.

108

Under this light, infectious diseases do not represent the lower stage in the progression of disease patterns as it was predicted by the epidemiologic transition paradigm (11). There is no linear and mandatory transition from communicable to non-communicable diseases, so there is no irreversible shift in the causes of disease and death. Even though, at first sight, many diseases seem to be typical of the pre-industrial or post-industrial era, a holistic approach reveals another story: human disease patterns depend on multilevel impacts produced by humans on the environment, as well as on ecological dynamics and contingent events. Exploring the influence of human activities and economic processes on landscape and pathogen dynamics, would be vitally important to prevent a large part of infectious diseases.

An epidemiological overview on communicable and non-communicable diseases

It should be noted that a sharp distinction between communicable and non-communicable disease is no more taken for granted. Diseases that once were thought to be non-communicable have been found to have infection causing cofactors, and viceversa.

According to the World Health Organization (17), around one-fifth of all cancers worldwide have shown to be linked to chronic infections by agents like immunode-ficiency virus (HIV), human papilloma virus (HPV), hepatitis B virus, and *Helicobacter pylori*. Conversely, degenerative diseases and their treatments may alter the immune system of individuals leading to associated infections that complicate the clinical work.

Focusing on the epidemiological data of the last two decades, some interesting trends can be traced. In 2010 there were 52.8 million deaths worldwide and 24.9% of them were charged to communicable maternal, neonatal, and nutritional causes (http://www.hsph.harvard.edu/news/magazine/shadow-epidemic). In 1990, such percentage was higher of 34.1%.

On the other hand, deaths from non-communicable diseases showed an opposite trend, rising by 8 million between 1990 and 2010, accounting for two of every three deaths (34.5 million) worldwide. In the same period, 8 million people died from cancer, that is 38% more than two decades ago.

While infectious diseases do not show signals of retrieving, ageing and growth of world population imply a progressive increase in the global cancer burden. However, population ageing can just partially account for the general increase of cancer incidence and cannot account for it in young people. For example, there was an evident increase of cancer incidence in childhood and adolescence during the past decades, with an increasing rate of this trend more recently. In order to explain these data, some authors have suggested that dangerous exposures occur in critical periods of the embryonic development, or during childhood and adolescence (18). Moreover, the environmental factors can become embedded in the biology of humans due to durable epigenetic alterations that modify patterns of genetic expression in individuals (19).

In the Nineties, age-standardised incidence rates were 140 per million in age class 0-14 years and 157 per million in age class 0-19 years. Over the last three decades, overall incidence increased for most tumour types by 1.0% per year in children, and by 1.5% per year in adolescents (15-19 years). The most evident increases were recorded for carcinomas, lymphomas, and germ-cell tumours. The expected changes in global population of the next two decades suggest that even if the current global cancer rates remain unchanged, the incidence of 12.7 million new cancer cases in 2008 will rise to 21.4 million by 2030 (20).

The challenges of tackling cancer are enormous and policies for primary prevention should be encouraged. Some evidence suggests that a pervasive deterioration of the environment and lifestyles can play an important role in promoting this trend of cancer. Not surprisingly, the global burden of cancer and other non communicable diseases is unquestionably expected to increase in the next few decades (19).

Cancer and the reductionist/determinist dogma

A major epistemological reason why biomedical sciences have neglected for a long time the environmental effects on human carcinogenesis arises from the fact that most biological research of the last century suffered from a pervasive reductionism (21, 22). In a significant part of the traditional studies in life sciences, the environment was thought to play a negligible role. All biological phenomena were seen to be under a strong control of genes, and well documented cases in which the environment deeply regulates human and animal development were considered as 'oddities' (23). The large amount of signals moving from the extracorporeal milieu of the organism to the internal one was relegated to a marginal position of regulating factors and processes. Even today, the reductionist biology perceives the environment just as a set of surrounding conditions (i.e. temperature, pH, oxygen, etc.) which establish whether or not the organisms are authorized to survive and develop. Once the environmental authorization has been given, all information required to enable a fertilized egg to become a complete individual would be present in its genes (the input) (23) and transferred directly to its phenotype (the output). In other words, the development would be a simple translation of instructions fixed in a codified program, that is the genetic makeup of a fertilized egg.

According to such gene-centered assumptions, the development of humans and other metazoans is often thought of as being 'program-driven' so far. However, this

view is misleading because it does not reflect the real manner in which living beings organize themselves and develop (24). A program-driven process needs that all the information held in the program (the DNA) be present in advance; furthermore it needs i) to be able of congruent actions and reactions to a large variety of environmental contingencies, ii) to be non perishable, and iii) to be checked continuously. Conversely, an 'execution-driven' process does not require all the information be available in advance, even if it produces similar outcomes in some general respects (i.e. similar phenotypic architectures in individuals of the same species). In complex biological processes like development, both information and dynamics are the result of new structures and interactions generated during a previous stage, leading to new range of possibilities and constraints. This new stage gives rise to emergent properties and draws the paths to next stages in the construction of the organism's phenotype. Complex biological systems develop mainly by such execution-driven processes, as shown by important data on protein folding and misfolding (24).

As a result of recent successes in sequencing genomes of many complex organisms, it has been shown that the number of genes is too low to predetermine the course of their development and their diseases, morphological properties and other traits. In other words, there is no one-to-one correspondence among the genetic makeup of an organism and its resulting phenotype (22). Currently there is a growing amount of biological evidence on the fundamental role of the environment in controlling the organism phenotype. This point is very important to clarify some trends in both biomedical sciences and health policies. Promoting a predictive, genetically individualized medicine instead a public, structured action on the ecological (socio-economic and environmental) factors to prevent chronic diseases appears to be a side effect of the old biological reductionist/determinist dogma 'one gene - one protein' and of the absurd separation of human health from human ecology.

The most important consequence of what mentioned above is a regression from a universally accessible public health system to a dramatic race to private and individualised solutions (6). In other words, the problem is that this paradigm considers human health just as a piece of the GDP.

Ecology and economy

Today we live in a globalized world where the economic growth paradigm is ever more widespread. Orthodox economists operating within this economic framework believe that living nature is an indestructible capital asset and that GDP is capable of growing indefinitely thanks to our technological power in exceeding natural constraints and enhancing human condition (25). This belief has strengthened the idea that human happiness is allowed by individual initiative and private appropriation (6), regardless any culture of conviviality and common goods. Therefore, the precept of the economic growth per-

vades all levels of political agendas as well as international conventions, multilateral agreements and important traties, including those aimed to pursue environmental quality, social equity and global peace.

A linguistic icon of this ideology is well epitomized by the rhetoric of 'sustainable development': a misleading concept that is largely used (also by professional ecologists) for justifying the supremacy of economic growth under the reassuring aegis of environmental and social justice. A short list of examples can be much more eloquent than any conceptual sentence.

Biodiversity loss rates are increasing and the Convention on Biodiversity has shown not to be effective in protecting the biosphere. Kyoto Protocol has not reduced greenhouses gases and global warming is ever more challenging. Global development programs have not removed the gap between rich and poor countries. The non-proliferation treaty has left us with more nukes, more countries possessing nukes, more sophisticated nuclear weapons. The myth of Green Revolution has reduced food sovereignty and security, preventing farmers from adopting sustainable crops and growing methods. Millennium Development Goals appear not to be achievable (26).

It seems that the institutional awareness of the environmental crisis supports, rather than fights, energetic consumption, poverty, chemical contamination, artificial settlements, biological exploitation, and thus supporting, at least indirectly, health risks. The international policies appear to be subordinated to the economic precepts of commodification of all material and immaterial needs, including primary goods and social values.

The current economic approach to the environmental and health crisis is ineffective because is wrong. It relies on the false assumption that the planet ecology is a small part of human economy, rather than viceversa. A rough prejudice supporting this anthropocentric vision is not that the natural world was created for man, but that it was created for a development model based on commodification and over-accumulation. This model entails a science as a technocratic tool that separates the functioning of the real world in thousands of mechanisms, included the separation between living beings and ecological context. Science is also fragmented in thousands of disciplines or specialities and, not rarely, its results are privatized or patented by industry. The owners of scientific knowledge try to establish the boundaries of the scientific mainstream and how to plan the research agenda, providing also the contents and requirements of scientific work, the rules for who is recruited and who is not, the domain of acceptable theories, and the vocabulary for dismissing inconvenient ideas as 'unproven', 'obscurantist', 'ideological' or something similar. They often have the power of censorship, creating a scientific bureaucracy and developing the art of public decision depending on private interest. Even though disclosure statements can mitigate the negative effects of conflict of interest within the scientific literature, this abnormal condition can affect the formal validation and peer-review practices. Therefore, the conflict of interest is still considered an unavoidable byproduct of the scientific profession.

The integrity and public credibility of academic work are at risk, as the conflict of interest encourages the social skepticism about scientific and technological applications such as drugs and other products. Moreover, the scientific conflict of interest – that is the overlapping interest among corporations, international agencies, universities, major foundations, honorary societies, think tanks, and prestigious journals – has created a kind of nomenclatura that can influence negatively the decision making processes by producing technocratic drifts that run against the commons and public interest (26).

Human niche construction

The scientific literature looking at the ecological foundations of public health is increasing. Such a trend is mostly supported by evidence emerging from basic investigation in life sciences, indicating that a feedback loop binds organisms and their environment. This feedback loop gives rise to an interplay that several ecologists call 'niche construction' (27). While the adaptionist view of the organism-environment relationship relies on the assumption that living beings 'propose' solutions to solve problems posed by an autonomous environment (13), a niche construction-based approach suggests that the pressures of natural selection cannot be considered as forces independent of the same organisms on which they act. Many cases show that organisms belonging to a variety of taxa may actively contribute to shape the local conditions of the environment in which they are selected. For example, by dam construction, beavers (genus Castor) modify the structure and dynamics of riparian environments and create local wetlands that can persist for a long time. In this way, these rodents affect natural selection pressures on their descendants, who can inherit similar environmental conditions for an indefinable number of generations.

One of the most important examples of niche construction on a global scale is provided by the role played by ancient photosynhetical organisms who led the air concentration fraction of oxygen to 21% during millions of years. According to these and many other proofs, living beings not only adapt to their environment but also contribute to construct it producing a sort of 'ecological inheritance'(27).

The darwinian teaching revised in the light of the new organism/environment interaction approaches shows that *Homo sapiens* contributes to his niche construction by altering the environment, just as other species do (28). The problem is that human beings modify the ecological conditions in which they and their offspring live and develop in a way that never been done before.

De facto, humans have extensively altered the global environment, affecting biogeochemical cycles, modifying the properties of soils and territories, increasing the biodiversity loss and enhancing the mobility of many organisms. In the last three centuries, the intensive consumption of fossil energy, along with the exploitation and clearing of forests, have increased the concentration of atmospheric carbon dioxide (CO2) by 30%, with more than 1/2 of

this increase occurring in the past 40 years. As stated by the WHO (http://www.who.int/globalchange/en/) and many other health agencies, the increased concentrations of CO2 and other gases that contribute to climate warming is a major factor of global instability and a new threat to public health. Chemical contaminants coming from agricultural, industrial and urban areas has increased pollution everywhere on the Earth, causing major ecological impacts on natural environments and human, animal and plant health.

In the last centuries, our species has deeply modified half of the ice-free land surface and converted prairies, forests and wetlands into rural and urban systems. Humans appropriate more than 30% of the net primary productivity on land and consume fish that use 8% of ocean productivity. Moreover they manage more than 50% of the available fresh water, but this percentage is expected to growth to 70% in the next 40 years. The growing potential of people to migrate and travel has impressively increased the vagility of organisms from/to all the regions of the planet. Together these and other changes have riduced the amount and diversity of the biosphere. Humans have induced the disappearance of 5-20% of the species in many taxa, and the ecological estimates tell us that the current rates of extinction are 100-1,000 times greater than natural extinction rates. Furthermore, most recent approaches to estimating next rates of extinction suggest further acceleration by a factor 10 or more (29, 30).

Dramatic and rapid changes in health and environmental culture are emerging at global scale, but this transition does not translate in real action of the International agencies and institutions. Meanwhile, nobody can say what could be the long-term ecological and societal consequences of the current economic model (31).

Human social ecology

As argued by Lewontin and Levins (32), 'the ecology of humans is a social ecology' that is becoming an ever more critical, ecological force interacting destructively with local, regional and planetary dynamics.

The main economic model worldwide is based on GDP and completely neglects the impressive costs of human activities. So it is clear that a basic discussion about the relationship between social and ecological systems should be developed around the foundations of the model, not about the solution that can be implemented within the model. It is worth noting that conventionally GDP takes no account of the role of ecosystem services and put under the positive values column the expenses aimed to remedy depleted and degraded natural resources. As a result, a country could clear its forests, deplete its fisheries, pollute its aquifers, causing a heavy damage in its ecosystems and threaten its human population, and this would be computed only as a positive gain in GDP, without registering the corresponding decline in assets, public health and wealth.

There has been a lack of research on how macro- and micro-economic determinants correlate with cancer inci-

dence, and how this relation varies by cancer type and country (33). So far many barriers exist to the understanding of global patterns of many diseases. However, a growing evidence shows a correlation between GDP and increased risk of chronic diseases such as cancer and others (34, 35). More pollution, greater consumption of processed foods, less time engaged in physical exercise, and other risk factors closely related to economic growth may partially explain why cancer rates are higher in countries with higher GDP.

The problem is that human health is both a product and a determinant of well-being and depends closely on the environmental health (34). Changes in the quality or quantity of environmental goods and services that regulate and influence food, air, water and land quality can have very important impacts on human health.

As emphasized by other works (10), environmental stress and deterioration induced by humans are increasing, and the impact on health of populations is more significant now than in any previous time in history. The general increase of cancer occurrence represents a byproduct (among many others) of an aberrant human ecology based on the myth of endless economic growth. The current sophistication of man-made environments reshape the biotic and abiotic environment and produces new patterns of human disease. Unfortunately, over the last decades, public health slowly drifted away from environmental concerns, progressively narrowing its focus on individual disease-centered intervention strategies based on selective case management or specific disease prevention technologies in groups at risk (10).

Given that biomedical researchers are not used to looking at their work within a historical and spatial perspective, usually they neglected the eco-evolutionary side of diseases. Such a bias prevented them from catching the basic relationship existing between public health and contextual determinants of human diseases.

Different societies living in different environmental conditions (climate, geo-morphology, fresh waters, vegetation cover, biological community, etc.) interact with them in different ways. The statistical structure of these man-made environments and the functional correlation among their components reflect the particular patterns of interaction of human ecology and public health. There is a clear indication that 'human ecology' – in the broad sense of environmental variables, lifestyles, culture, and social organization – has a predominant role in shaping cancer and other disease profiles (36, 37, 38, 39). The emergence of a new vision of human ecology can be seen as a reaction to the positivist approach in life sciences and the current economic model of environment-human interaction (10).

Conclusion

Human culture and technologies may act as a selective force affecting the environment, biology and health of both human and other species. Given the complex nature of our species, our ecological niche presents unavoidable, epistemic implications, which make up what we call 'human culture evolution'. The evolution of human culture involves – quoting Eva Jablonka (28) – 'changes in the intergenerational transfer of ecological legacies, in the reconstruction of developmental conditions, in the transmission of behavioural and symbolic information and in the selective stabilization of practices and preferences'.

As such, human culture can be viewed as a special and extreme case of niche construction, where human-specific cultural (economic, political, ideological and religious) beliefs meet with each other. This should provide the opportunity for rethinking the special kind of consequences that human niche construction produces on the organization of the environment and, therefore, on that of physical, mental and social health of our species.

References

- Livingstone FB. Anthropological implications of sickle-cell gene distribution in West Africa. American Anthropologist 1958; 60: 533-562
- Wiesenfeld SL. Sickle-cell trait in human biological and cultural evolution. Science 1967; 157: 1134-1140.
- May JM. The ecology of human disease, An. NY Acad Sci 1960; 84: 789-794.
- Levins R, Lewontin R. The Dialectical Biologist, Cambridge, MA: Harvard University Press. 1985.
- Galea S, Riddle M and Kaplan GA. Causal thinking and complex system approaches in epidemiology, International Journal of Epidemiology 2010; 39: 97-106.
- Vineis P. Public health and the common good, J Epidemiol Community Health 2014; 68: 97-100.
- Editorial. An Overdue Ban on Trans Fats, New York Times, 2013; November 11, (http://www.nytimes.com/2013/11/12/opinion/an-overdue-ban-on-trans-fats.html?_r=0).
- Dunn FL, Health and disease in hunter-gatherers: epidemiological factors. Reprinted in: Culture, Disease, and Healing: Studies in Medical Anthropology, 1977, Edited by Landy D, pp. 99-106. Macmillan. New York.
- Vineis and Pearce. Genome-wide association studies may be misinterpreted: genes versus heritability, Carcinogenesis 2011; 32, 9: 1295-1298.
- Pedersen D. Disease ecology at a crossroads: man-made environments, human rights and perpetual development utopias, Soc Sci Med 1996; 43, 5: 745-758.
- Omran AR. The epidemiological transition: a theory of the epidemiology of population change, Millbank Memorial Fund Quarterly 1971; 49: 509-538.
- Gould SJ. Wonderful Life: The Burgess Shale and the Nature of History, New York. 1989.
- 13) Lewontin R. Gene, organismo e ambiente, Laterza, Roma-Bari. 1998.
- 14) Carrel M, Emch M. Genetics: A New Landscape for Medical Geography, Ann Assoc Am Geogr 2013;s 103(6): 1452-1467.
- Frenk J, Gómez-Dantés O, Knaul FM. Globalization and Infectious Diseases, Infect Dis Clin N Am 2011; 25, 593-599.
- 16) Schaaf M. Confronting a Hidden Disease: TB in Roma Communities, Roma Health Project, Open Society Institute, Public Health Program. 2007.
- 17) WHO. Burden: mortality, morbidity and risk factors, in: Global Status Report on noncommunicable diseases 2010, World Health Organization Library. 2011.
- 18) Balbus JM, Barouki R, Birnbaum LS, et al. Early-life prevention of non-communicable diseases, Lancet 2013; 381: 3-4.
- Vineis P, Stringhini S, Porta M. The environmental roots of noncommunicable diseases (NCDs) and the epigenetic impacts of globalization, Environ Res 2014; http://dx.doi.org/10.1016/j.envres. 2014.02.002.

- 20) Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study, Lancet 2004; 364: 2097-105.
- Sonnenschein C, Soto AM. The society of cells: cancer and control of cell proliferation. New York: Springer Verlag. 1999.
- 22) Sonnenschein C and Soto AM. Cancer Genes: The Vestigial Remains of a Fallen Theory, in: Genetic Explanations Sense and Nonsense, Edited by Sheldon Krimsky and Jeremy Gruber, 2013, Harvard University Press, Cambridge, US.
- 23) Gilbert SF. Mechanisms for the environmental regulation of gene expression: Ecological aspects of animal development, J Biosci 2005; 30(1), 65-74.
- 24) Yates FE. x, Homeokinetics/Homeodynamics: A Physical Heuristic for Life and Complexity Ecological Psychology 2005; 20:148-179.
- Dasgupta P. 2013. Nature's role in sustaining economic development, Phil Trans R Soc B 2010; 365.
- Levins R. Why programs fail. Monthly Review 2010; (https://monthly review.org/2010/03/01/why-programs-fail).
- 27) Laland KN, Odling-Smee J, Feldman MW, Niche Construction, Ecological Inheritance, and Cycles of Contingency in Evolution, in: Cycles of Contingency. 2001, Edited by Oyama S, Griffiths PE, Gray DG, The MIT Press, Cambridge, US.
- 28) Jablonka E. The entangled (and constructed) human bank. Phil Trans R Soc B 2011; 366, 784.
- 29) May RM. Ecological science and tomorrow's world, Phil Trans R Soc B 2010; 365, 41-47.

30) Barnosky AD, Matzke N, Tomiya S, et al. Has the Earth's sixth mass extinction already arrived? Nature 2001; 471: 51-57.

- 31) Stuart Chapin F, Erika S, Zavaleta ES, Eviner VT, et al. Consequences of changing biodiversity, Nature 2000; 405: 234-242.
- 32) Lewontin R and Levins R. Preparing for uncertainty, in: Biology under the influence Dialectical Essays on Ecology, Agriculture, and Health, Lewontin R and Levins R, 2007, Monthly Review Press, New York, US.
- 33) Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study, Lancet Oncol 2012; 13: 790-801.
- 34) Grant WB. A Multicountry Ecological Study of Cancer Incidence Rates in 2008 with Respect to Various Risk-Modifying Factors, Nutrients 2014; 6: 163-189.
- 35) Coccia M. The effects of country wealth on incidence of breast cancer, Breast Cancer Res Treat 2013; 141: 225-229.
- Kartman L. Human ecology and public health, American Journal of Public Health and the Nations Health 1967; 57, 5: 737-750.
- Henderson WE, Craig CM, Holroyde G. Cancer in Westmorland: an investigation into its incidence epidemiology and ecology, British Medical Journal 1929: 1062-63.
- 38) Benigni R, Giaimo R, Matranga D, Giuliani A. The cultural heritage shapes the pattern of tumour profiles in Europe: a correlation study, J Epidemiol Community Health 2000; 54: 262-268.
- Sokal RR, Oden NL, Rosenberg MS, et al. Ethnohistory, genetics, and cancer mortality in Europeans, Proc Natl Acad Sci USA 1997; 94: 12728-31.

Correspondence: Carlo Modonesi, E-mail: modonesi@unipr.it