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Environmental Alteration Leads to Human Disease

A Planetary Health Approach

 Springer

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Foreword

Since the dawn of Medicine, the Hippocratic tradition has emphasized the need for harmony between every individual and the natural environment as the correct philosophy to maintain an optimal state of health.

This approach has been gradually overshadowed over the course of history, focusing on the disease first and then on the single patient. Only in the last decades, a renewed and growing attention has been paid to the environmental issues and their potential impact on human health. To date, environment is estimated to account for almost 20% of all deaths in the WHO European Region. Therefore, the environmental topics and their relationship with health problems have become a priority even on many governments' agendas.

Devastating effects of environmental pollution on global climate change are sadly known, with an increase in Earth temperature and the progressive desertification of many areas. Human beings are responsible for the large-scale fires that are hitting the Amazon rainforest, in particular large livestock and agro-industrial enterprises. Their actions are determining the livability of this place, extremely important and vital for the environmental balance of the whole planet.

In this context, the importance of environmental pollution in large cities is increasing more and more. Today, over 3 billion people live in metropolitan cities and megacities. It is estimated that in 2030 60% of the entire population will live in large urban areas, while in 2050 this number will be 70%. During the last 50 years, this unstoppable trend has been changing the face of our planet. This transformation must be evaluated in all its complexity; not only the socio-demographic aspects, but also the consequences of this migration on individuals and community's health. New habits and new risks changed and are changing the main causes of death in developed countries. In the last century, they faced the great challenges of viral infectious diseases. The important discoveries in the medical field contrasted their spread, leading to an increase in life expectancy and consequently to a rise in the world population, with the following creation of increasingly large and populous urban centers. On the other hand, this transformation has opened up the challenge to chronic noncommunicable diseases, today the main cause of mortality in developed countries. However, the ever-present risk of infectious diseases, which indeed spread much more easily in a globalized world,

should never be neglected, as the ongoing COVID-19 pandemic is sadly remembering us.

Today, there is a considerable awareness about environmental pollution and increased risk of cancer. However, little is perceived by the population on the relationship between other diseases, the environment, and its changes. We are observing a steady increase in scientific studies that are investigating the pathophysiological mechanisms of many chronic noncommunicable diseases and the correlation with environmental pollutants although much remains to be clarified. In particular, many studies are focusing on the so-called endocrine disruptors, substances able to impair the normal function of the endocrine system, causing adverse effects on the health of an organism or its offspring. These substances are derived from human activities, mainly from industrial activity, and are ubiquitous in the environment. Consequently, we are continuously exposed to them, even during our fetal life. They are able to bind several hormone receptors, acting as agonists or antagonists. Moreover, they can interfere with hormonal synthesis, secretion, transport, and elimination. Therefore, these compounds can cause severe damage to exposed organisms; their detrimental effects cannot be immediately noticeable because at low dosage they do not cause acute toxic effects. Birth defects and developmental, sexual, and cognitive disorders may be consequence of the exposure. Recently, reproductive disorders, some types of cancer, metabolic diseases such as obesity and diabetes, cardiovascular, skeletal, autoimmune diseases have also been associated with endocrine disruptors. Further studies are surely needed to carry out a complete risk assessment; in particular, low dosage exposure and the cocktail effect (the total effect due to the sum of the individual substances) must be investigated.

In addition, urbanization is also rapidly changing all our lifestyle habits, especially in the latest decades. Indeed, urbanization is producing a harmful "environmental stress": pollutants in air, water, and soil find weakened individuals. The combined action of these factors with other negative outcomes of urbanization, such as traffic and rhythms of life, can generate stress for our communities. As a matter of fact, in last decades stress has become one of the most common disorders in developed countries. Rhythms imposed by urbanization may alter our "biological clock", making subjects more fragile. Recent evidence suggests an association between circadian rhythms and the psychoneuroendocrine system, with a role on the pathogenesis of diseases such as obesity, type 2 diabetes mellitus, tumors, neurodegenerative and immune system disorders. Humans have a complicated organization, which includes social habits, traditions, and culture. Today, we know that healthy eating and adequate sleep are the best tools to ensure a good metabolism. It's not just about what or how much you eat, but also *when*. The stress induced by eating food at the wrong time for our metabolism is enormous. At the wrong moment, the body is unable to correctly metabolize food and therefore stores it as fat. Urbanization has radically changed eating habits. The same applies to sleep, the duration of which has decreased by about 2 h in urban areas over the last 50 years.

Consequently, considering all new emerging data, it is necessary to further investigate the role of the environment in human diseases, with a global approach. Even the current definition of disease seems out of date. It should be remembered that in 1948, in the aftermath of the Second World War, founders of the World Health Organization defined health as a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity. Today, a more modern and appropriate definition should take into account that our health depends on genetic predisposition for 20% and on environmental factors for 80%. Treatments must necessarily go beyond the single person and the current concept of disease, studying at the same time the surrounding context of life and the community. Therefore, we must move from the concept of a patient-centered medicine to a broader concept of community-centered medicine, up to an even wider approach, a **planetary health approach**, focused on health as a common good of a "planetary" community. The challenge in the coming years is epochal and will necessarily lead to broad reflections in terms of politics and health planning. Personalized medicine certainly remains the future, but we must not neglect the totality of the individuals and the communities. Community-centered medicine means also that doctors and researchers must overcome the current health care system and closely collaborate with other experts, such as those in environmental issues. A biomedical approach is then necessary in order to face the great challenges that phenomena such as globalization, socio-demographic growth, and urbanization will bring in the health care system.

Planetary Health is interdisciplinary, but first of all it must be systemic and it needs a preferential relationship between Ecology and Medicine. This relation is to be upgrading because today both ecology and medicine pursue few systemic characters and few correct interrelations. We need to refer to new principles and methods sustained by the most advanced fields, as Landscape Bionomics and Systemic Medicine.

Thus, we will be able to better discover environmental syndromes and their consequences on human health. Environmental transformations proposed by Planetary Health Alliance, at Harvard University, from biodiversity shifts to climate change do not consider bionomic dysfunctions which can menace human health. On the contrary, finding advanced diagnostic criteria in landscape syndromes can strongly help to find the effects on human well-being. The passage from sick care to health care can't avoid the mentioned upgrading. We must refer to an ecological upgraded discipline, the Landscape Bionomics, emerged following the present shift of scientific paradigm from reductionism to systemic complexity. The first consequence is a new concept of life, not centered on the organism but on the entire "biological spectrum" made of a more defined gradient of living entities, each one strictly interrelated with and interdependent on the inferior and superior ones.

The aim of this book is to analyze the most recent scientific data regarding the complex relationship between environment and human diseases. It is the

first book that has this very interesting and extremely difficult goal. I would like to thank all the authors who participated and contributed to its creation, with the hope that it will be the forerunner of a new chapter in the Medical Science.

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Preface

Environmental alteration leads to human health: but the term environment is, today, a misunderstood word, abused, and very often used in a not scientific sense, even in medicine. The concept of environment is mainly intended as hydro-geological and climatic influences, human urbanization and pollution, while it regards firstly the so-called Biological Spectrum (sensu Odum, 1971) that is the hierarchic levels of biological organization: from the ecological communities to the landscape's units and the eco-regions.

Traditional Biology focused on small scales (from biomolecule to the organism) is still mainly reductionist, so marginalizing macro-scales (from community to landscape and biosphere). Medicine seems to be interested in Traditional Biology: the study of pollution and its effects of our health reached today an increasing importance analyzing endocrine disruptors, while very few researches are related with landscape vegetational dysfunctions. Nevertheless, the "rock in the pond" of the systemic turn in scientific paradigms imposes to change our vision: biology does not concern only micro-scales.

We can see that the biological studies on bio-chemical molecules, genetics, viruses, and metabolism led to many successes, but also made insidious errors as, for instance, the statement of DNA as the "central dogma of molecular biology," wrong because the DNA is not a set of formed characters but a set of potentialities. Another tricking error is just the marginalization of macro-scales, which brought to refuse a proper scientific role to the researches in this field.

In Medicine, we can see two reactions: (a) many researchers think even today to the fallacy of ecological aspects in etiology, and (b) some doctors appreciate the problems that come with environmental degradation but, generally, *see them as someone else's problem to solve*, while they focus on *repairing* the damage. Therefore, it is not entirely clear what the medical profession/students are meant to "do" with the ecological problems and how they can use them to help patients.

However, recently, some medical communities recognize that human alteration of Earth's ecological systems threatens humanity's health, as underlined by the recent MACH (Centre for Multidisciplinary Research in Health Science, University of Milan, coordinated by M. Raviglione) and One Health, Global Health, and Planetary Health scientific associations, e.g., PHA (Planetary Health Alliance, Harvard University). All these medical

associations are interdisciplinary while, first of all, they must be systemic and pursue a preferential relationship between advanced Ecology and Medicine.

This misunderstanding between Medicine and Ecology is a challenge: we must overcome this impasse! Thus, we cannot discuss the unity of life, but we have to understand better how its scalar interrelations may influence our health. The alterations of life at macro-scales can damage human health, not unlike at small ones. Note that the underestimation of the environment is rooted in Neo-Darwinian's thinking, where the struggle for existence is considered more important than the symbiosis and cooperation. Especially crucial is the *epigenetic* control of gene expression due to DNA methylation. It demonstrates that the phenotype is not directly expressed by the genotype, and part of the genome's methylation pattern can be inherited in the Lamarckian sense.

The dependence of gene expression on the environment is now clear, as confirmed by Psycho-Neuro-Endocrine-Immunology. We move from a mechanistic vision to a complex and systemic one: not only what is written in the *sequence* of the DNA bases matters, but also their modulation due to the information that the *environment* and behavior express. We can see that overcoming the mentioned misunderstanding between Medicine and Ecology needs a theoretical premise on Landscape Bionomics and example of application that correlates bionomics, landscape health, and a disease's incidence. These observations explain the sequence of the first six chapters (and the addition of the 15th one): (1) *The systemic paradigm in Biology* (M. Bertolaso, P. De Felice); (2) *A new Paradigm in Medicine: Psychoneuroendocrineimmunology and Science of Integrated Care* (A.G. Bottaccioli, F. Bottaccioli); (3) *From general ecology to Bionomics*; (4) *Planetary Health: Human Impacts on Environment* (V. Ingegnoli, E. Giglio); (5) *Landscape Bionomics Dysfunctions and Human Health* (V. Ingegnoli); (6) *Agrofood systems and Human Health* (S. Bocchi, M. Raviglione); and (15) *Some landscape and healthcare considerations comparing European Union and Indian Federation* (V. Ingegnoli, E. Giglio).

Only partially following this premise are Chaps. 7 and 8, anyway, concerning important contents: *Environmental alterations and oncological diseases* (C. La Porta) and *Zootechnical Systems, Ecological Dysfunctions, and Human Health* (L. Bonizzi, F. Campana).

The Planetary Health Approach of this volume is essential to understand the complex relationship between every component of the biology, as well as physics on Earth life.

At the microorganism level, as an example, we underline what is the impact of environmental alterations on human microbiota, the complex and diverse community of bacteria, archaea, fungi, protozoa, and viruses that live on and within human beings. This relationship (Chap. 10: *The impact of environmental alterations on human microbioma and infectious diseases* by D. Barbato, C. Sestili, L. Lia, A. De Paula Baer, and G. La Torre) put in evidence that as human being we are not only what we eat, but also what we breathe and drink in the broadest sense.

Moreover, the relationship between environmental conditions and mental well-being has been acknowledged and has recently garnered additional

attention in the face of climate change. In this chapter (Chap. 11: *The relationship between environment and mental health* by R. Cocchiara, A. Mannocci, A. De Paula Baer, and G. La Torre), we try to explain the main potentially associations between the mental illnesses and heavy metals, the climatic factors, and indoor environment. Following this approach, we give an overview on new psychological effect of ecological crises, such as eco-anxiety, ecological grief, and solastalgia.

Finally, the One Health Approach is very consistent with the Planetary Health Approach. In Chap. 12: *Planetary health for clinicians* (G. La Torre, B. Dorelli, and A. De Paula Baer), the One Health Initiative is presented as a worldwide strategy to increase inter-sectorial collaborations in all aspects of health care for humans, animals, and the environment, with the aim to “forge co-equal,” all-inclusive collaborations among physicians, veterinarians, nurses, and other scientific-health and environmentally related disciplines.

Further topics with impact on both ecological and biomedical level are discussed in the other chapters. A particular mention is required for the endocrine disruptors (Chap. 13: *Endocrine Disruptors and Human Reproduction* by F. Pallotti, D. Paoli, M. Pelloni, and F. Lombardo), chemicals capable of interfering with human endocrine system at multiple levels. An old story that has become recent news, these chemicals are by-products of human and modern life industry (plastics, flame retardants, cosmetics, pesticides, etc.). Since the last century, these substances have become a relevant public health issue, forcing governments to strictly rule their use. Nonetheless, their widespread use and persistence in the environment have led to measurable consequences in terms of endocrine disease incidence, reproductive health problems, and even cancer.

Endocrine disrupting chemicals also appear to have epigenetic effects capable of being transmitted over the subsequent generations, thus requiring to increase our awareness and vigilance.

Due to extreme interest raised in the scientific community, as one of the most widespread noncommunicable disease, the *Environmental factors in the development of diabetes mellitus* (Chap. 14 by Laura Nigi, Caterina Formichi, and Francesco Dotta) also will be mentioned in this book.

Diabetes mellitus is a global health issue, with a multifactorial pathogenesis. Recently, a great interest has been focused on the environmental factors associated with the onset of the disease, from the best known lifestyle factors, such as diet and physical activity, to environmental pollution and gut microbiome. It is now evident that epigenetic modulation has a pivotal role in determining the phenotype of genetically predisposed individuals in response to environmental factors. Epigenetic changes can occur both in utero and after birth, influencing the onset of chronic diseases, such as diabetes mellitus, in adulthood. Indeed, it has been demonstrated that these new actors in diabetes pathogenesis could represent promising therapeutic targets.

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31 July, 2021

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Understanding Complexity in Life Sciences

1

Marta Bertolaso

Abstract

In this introductory chapter I will discuss why in the biological sciences reductionist perspectives often prevent science from making the most of its own empirical evidence and findings. Scientific knowledge in biological sciences, in fact, is mediated by questions that deal with inter-level regulatory processes and emergent complexities that change the causal dynamics relevant to understanding and intervening in living systems' functional states and dynamics. In this contribution I will thus go through some features of systemic thinking and I will discuss some epistemological implications of its use in the life sciences in their wider sense. Overcoming reductionist ontological and epistemological assumptions in scientific practice can open up new possibilities for scientific and technological advancement.

Keywords

Complexity · Integration · Mesoscopic way of thinking · Relational epistemology

1.1 Introduction

Philosophers and scientists alike have been discussing for decades what possibilities we have in scientific practice to offer simple explanations of complex phenomena like collective behaviors of animals, cells, and organisms more in general. Such simplifications have often acquired the form of a reductionist way of thinking about biological dynamics and living systems. This reductionist approach is usually articulated at three levels: ontological, for which any biological entity can be eventually represented by its more fundamental elements; epistemological, so that the explanations can be offered at what is considered the most fundamental level of organization of the systems; methodological, so that we can proceed through progressive decomposition of the systems to elaborate a model that can adequately represent the system itself (Brigandt and Love 2017; Bertolaso 2013; O'Malley and Dupré 2009). Despite the expectations of such a reductionist approach, which date back to the earliest complex systems theories, a completely different and systemic trend emerged in the last century for the life sciences. This systemic trend is not

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merely opposed to reductionism but has been looking for its own epistemological foundations and legitimation in biological sciences, economics, and social sciences (Donati 2009; Aguirre 2013; Bertolaso 2016).

In the same period, empirical evidence challenged both the possibility and the adequacy of a reductionist approach in scientific practice understood as the process by which scientists weighted their evidence and elaborate explanatory models. While, for example and more concretely, some diseases can be clearly traced backward and thus causally explained in terms of a specific molecular function that has been compromised (e.g. diabetes related to genetic mutations), other diseases are still defying such attempts. Clear examples are complex and chronic diseases, such as cancer and Alzheimer's. What prevents cancer, in fact, from being considered a disease reducible to one or more molecular factors and their alteration is the striking heterogeneity of molecular manifestations and characteristics, their heterogeneity over time, and the intrinsic feature of cancer to be able to compromise all levels of the biological organization of a living system. These features clearly prevent scientists from being able to offer simple explanations and a suitable and encompassing definition of cancer. This has consequences at the clinical level in relation to both diagnosis and treatment. Some unanswered questions include: in what sense can biologists and physicians consider a gene, for example, as being sufficiently explanatory of the overall disease? How are ideals of causal specificity simply bad epistemic ideals? Or, how do they hide an ignorance of molecular and genetic features not yet discovered? What does this imply, from a conceptual and explanatory point of view, assuming that the microenvironment plays a role in the failure or reconstruction of proper biological functions? Given these and other related questions, current reflections—both in the scientific and philosophical spheres—are urging a more radical epistemological change in the way of thinking which might be relevant not only for cancer but also for other organizational levels of biological and social entities and organizations (Urbani Ulivi 2011, Green and Batterman 2017, Bizzarri

2020). Forcing science to fit reductionist standards, in fact, seems to prevent science itself from making the most of its own empirical results.

In this chapter I will follow a narrative aimed at familiarizing the reader with some historical reasons and frameworks in both the reductionist and systemic ways of thinking while developing an argument that shows what perspective we could adopt to make sense of complex dynamics and of tensions generated by the previously adopted reductionist approaches in life sciences. In concrete, I will show (Sect. 1.2) how scientific knowledge in biological sciences is mediated by questions that deal with inter-level regulatory processes and emergent complexities that change the causal dynamics that are relevant for understanding and intervening in the functional states and dynamics of living systems. I will then offer (Sect. 1.3) an overview of current systemic views and introduce some main features of a systemic way of thinking, and I will discuss some epistemological implications of its use in the life sciences more in general (Sect. 1.4). Particular attention will be paid to the lack of time scale separation among and within levels of organization in living systems and its main epistemological implication. Overcoming reductionist ontological and epistemological assumptions in scientific practice can open up new possibilities of scientific and technological advancement (Sect. 1.5).

1.2 Where we Are Now: The Systemic Paradigms

Any time we try to understand complexity in biological and life sciences we are faced with a double tension. On the one hand, any concept implies referring to properties of an entity that are the result of correlations among its elements and subsystems at different levels of the entity and also of the interrelations that hold between the entity and its surrounding or (micro)environment. This can be true both in the case that the properties of each factor that plays a role in the emergent complexity remain qualitatively the

same (as in the organization of an industry, a group of people, some kind of biological and ecological system, such as a colony of animals) and in the case that properties of the elements are functionally or ontologically (permanently) modified once they are embedded in a specific environment or once their functional integration is compromised. I want to adopt this perspective because I think that a privileged perspective from which we can understand the epistemic and ontological foundation related to our understanding of biological complexities relies very much on our possibility to understand the kind of dependencies we try to modelized and explain. This obviously will determine also the specific approaches we will adopt in trying to deal with and manage the overall emergent dynamics. It will also shed light on other notions and concepts like plasticity and robustness that typically reflect the intrinsic features of a dynamically stabilized functional state that characterizes living systems or entity. In this sense we are thus considering different kinds of complexities widely discussed in literature over the last decades (Weaver 1948; Wimsatt 2007; Mitchell 2009; Bertolaso 2013; Dupré and Nicholson 2018) (Fig. 1.1).

On the other hand, the current coevolution of science and technology is forcing us, from within science itself, to elaborate new multilevel and complex models when we are dealing with complex systems whose adequateness is, nevertheless, often questioned (1) when we are dealing with the organizational and evolving features of living systems, and with their persistence in space and time and when (2) data clearly show that they are not self-evident or neutral in explanatory terms. I am thinking, concretely, of the current difficulties in evaluating social and economic trends, and of the limits that, for example, human genome sequencing has shown in interpreting and predicting cellular and biological behaviors at different levels of biological organization. I have discussed these issues more extensively elsewhere, but what is relevant for us in this chapter is to consider that at the crossroad of these challenges there is a question about what should be considered relevant in explanatory terms when describing and explain-

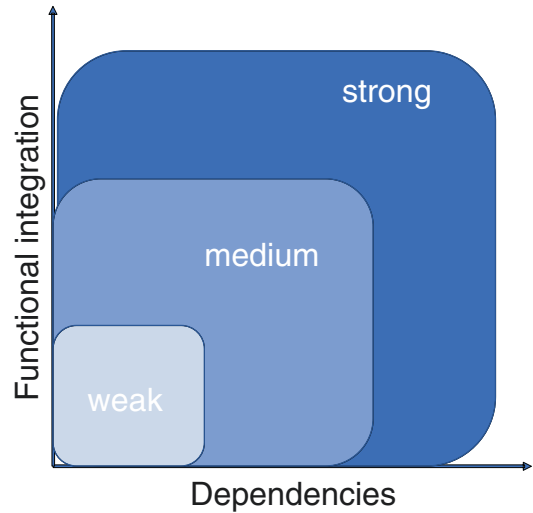


Fig. 1.1 The graphs represent how the progressive integration of functions correspond to different kinds of dependencies. Weak: an example are cells in a petri dish; Medium: an example are the dynamics that determine the normal functioning (topological dependent) of beta-cells; Strong: an example are the dynamics that determine the normal development of the organism and that typically are compromised in cancer, i.e. a genetic drift and genomic instability follow a functional dis-integration over time of the normal activity or differentiation processes of cells at specific levels. Space and time are diversely relevant in these processes as is their combined resultant in terms of microenvironmental features and topological organizations. Similar scales can be easily adopted for social, economic, organizational fields of inquiry

ing *inter-level regulatory processes*. It is, in fact, clear that a “most fundamental level” in explanatory terms cannot be identified in absolute terms and that an integral and relational epistemology is required to account for biological dynamics and behaviors, requiring new perspectives in order to guarantee a much more fruitful and sustainable development of the digital biotech field as well (Leonelli 2015). A systemic view of nature, based on complexity, seems to have a paradoxical existence in this case because, on the one hand, it seems to merely offer vague metaphors about “holism” and “networks” made all the more abstract by mathematical analysis; on the other hand, emerging technologies tend to become the norm for global and systemic analysis without a real impact on

our capabilities of anticipating and managing complexities and therefore of understanding them.

In what follows I will refer to the first tension as “tension about complexity” and to the second as “tension about the explanatory relevance of models.” I suggest that in the case of the reductionist expectation, simplicity in science and in life sciences goes with a mereological view of the natural world, and with a reduction *at unum* of the explanatory models, that is, a simplification of the systems in terms of some specific parts or elements, which implies an epistemological reductionism of scientific knowledge usually through a mechanistic understanding of causal dynamics and movements or changes in the living worlds. One example of this is the historical path that the war on cancer has taken. Since U.S. President Richard Nixon declared the “war on cancer” in 1971, various attempts at evaluating the overall progress of cancer research investments have been made. In 2010, cancer was still defined as a key public concern and a tremendous burden while the World Oncology Forum in 2012 asked if we were winning the war on cancer at all. Evidence about the lack of improvement in survival rates 1985–2007 (Pal et al. 2008), the small increases in life expectancy (Langer et al. 2015), and the rare enduring disease-free responses (Hanahan 2014) obviously posed questions about the strategies we were adopting to understand and manage such complex disease and whether it was adequate to look for the “enemy bases” or molecular entities to be targeted by means of more and more precise drugs (Soto and Sonnenschein 2011) or if “killing undesired cells” is the most promising focus. However, the turn toward a proper understanding of what it means, for example, to think of cancer in processual terms and not merely in terms of selfish genes or crazy cells is taking a huge effort and a long time (Huang 2011). Obviously, it is not surprising that also the question about whether or not high-throughput technology performs better in predicting and managing complex diseases still awaits a satisfactory answer and evidence (Geman and Geman 2016). Are we misguided?

1.3 How we Got Here: Struggling with Organized Complexities

“Something important about complex wholes is lost if they are conceived solely in terms of their least parts of which they are in fact composed” (Greene and Depew 2004, 311). To understand better the meaning and specific contents of these words, let us look at their history and go deeper into the trends and systemic challenges I have highlighted in the previous section to make explicit the main features of a systemic thinking.

As Warren Weaver stated in 1948, it seems clear that “SCIENCE has led to a multitude of results that affect men’s lives (...) men’s ideas and even their ideals” (p. 536). In particular, decades ago physical sciences had already started developing new conceptual and methodological tools when *problems with simplicity* started: “Living things are more likely to present situations in which a half-dozen, or even several dozen quantities are all varying simultaneously” (ibidem p. 537) resulting in nonlinear and collective dynamics. This challenge became even more evident when new tools like powerful techniques of probability theory and statistical mechanics to deal with many variables were applied to living entities that likewise cannot be “understood as a whole that merely possesses certain orderly and analyzable average properties” (ibidem p. 538). Weaver defined these problems as *problems with disorganized complexity*. Finally, *problems with organized complexity* lead the way toward a more comprehensive understanding of a systemic perspective to account for typical living systems’ dynamics. Dealing simultaneously with a “sizeable number of factors which are interrelated into an organic whole” asks for a focus on relationships in a “complicated but nevertheless not in helter-skelter fashion” as typically seen in cancer, finance, problems of tactics, and strategies (ibidem p. 541).

Using mantras that have been attributed to Einstein, we are allowed, especially in life sciences, to “make things as simple as possible, but not simpler” and not to stop thinking! Paradoxes, in fact, emerge any time we try to force epistemic reductionisms to account for inter-level regula-

tory processes, which are, in my view and understanding of living systems, the main feature that asks for a systemic explanation of dynamics and functional states dynamically stabilized in living entities like growth and development (see, e.g. Bertolaso 2016; Bertolaso and Dupré 2018).

Such paradoxes fall mainly into the following categories: (a) Difficulties in accounting for time dependent processes and causalities, that is, for changes that are intrinsically regulated by factors that are established in time later than the elements that constitute them. An example is the influence in regulatory terms of the microenvironment of a tissue that entails non-biological factors like collagen and matrix constituents or the overall production of insulin in beta-cells that is very much related to the topological structure of the islets of Langerhans (Loppini et al. 2014), etc. Examples can be equally derived from ecological and social sciences in relation to the impact of cities and landscapes on their populations, their life styles, or on social behaviors and resilience, etc. (b) Difficulties in understanding the (ir)reversibility of biological processes when they are attributed to intrinsic properties of the elementary constituent of the systems themselves, that is, when the causal explanation relies upon a mechanistic and atomistic (mereological) assumption. Typically, this happens when an attribution of function, which is a typical epistemic operation in life sciences, coincides with an ontological reductionist assumption for which activities belong to fundamental unities or entities as such (in this sense, for example, tumor cells have and retain the properties to proliferate abnormally, to avoid apoptosis, etc. independently of other (micro)environmental factors). This is well represented also by the paradox that emerges in cancer research when accounting for carcinogenesis on the basis of DNA's mutations where quite often the same genes are involved in oncogenetic or tumor reversion processes or even seem to follow more than anticipated neoplastic transformation of the cells. This approach was typical within the so-called central dogma of molecular biology that still sometimes grounds explanations of how biological information flows from genotype to phenotype, that is, the linear

causal relationship between a gene and a phenotype through the proteins machine. These explanatory approaches soon showed their pitfalls but a way out from those paradigms was slow to emerge due to their epistemological assumption. As Weinberg (2014), observes: “*Cell* has celebrated the powers of reductionist molecular biology and its major successes for four decades (...) [We] have witnessed wild fluctuations from times where endless inexplicable phenomenology reigned supreme to periods of reductionist triumphalism and, in recent years, to a move back to confronting the endless complexity of this disease.”

My thesis is that a way out from these tensions is much easier if we adopt a bionomics perspective. Such bionomics perspective inherits from the traditional systemic views the emphasis of the emergent properties of a system as a result of interactions and interrelations among elements framed in peculiar systemic characters (i.e. measured through specific systemic parameters), more that on elements' activities and properties but also ask for a reflection on time and space-time scale dependencies and integrations which also involve, for example, non-biological factors (e.g. stroma in biology, and geography in ecology, transports and infrastructures in social sciences) like in the case of the tissue constitution and maintenance in an organism or for the establishment or of the sustainability of a wide bioecological level at higher scales.¹

Although paradoxes seem to show limits of scientific and technological approaches and push researchers back in their efforts, we must also

¹I need to disentangle a couple of points on this topic. The first one is that I prefer not to use the concept of ecosystem in this context because it is often ambiguous, not being able to reconcile biotic and functional points of view and dependencies among space-time scales, which characterizes the principle of emerging properties (see also Ingegnoli 2002). Second, in this and other volumes it has been already discussed how *bionomics principles* (Ingegnoli, 2015) underline the difference between what really exists (Life on Earth hierarchically organized in Living Entities) and the different approaches to the study of the environment, transforming the main principles of traditional ecology by being aware that hierarchical levels are types of complex biological systems.

acknowledge that paradox-driven research has always shown itself to be more effective than mere technology driven research in disentangling issues, in showing the compatibility of different models and their possible integration at least at the epistemic level (...). They force us to look at the system as a whole and to focus on the functional capabilities that dynamically emerge when multiple elements interact simultaneously (among other authors we suggest the reading of the work by these authors: Waddington, Needham, von Bertalanffy, Denis Noble, Sui Huang, Gilbert, John Dupré, William Wimsatt, Sandy Mitchell). Moreover they are more capable of making sense of top-down causation and dynamics and of their relationship and possible integration with bottom-up processes, opening up a way from the shortcomings that the two types of paradoxes we have focused on in this section seemed to create.

1.4 The Way out: The Mesoscopic Way of Thinking

As I already discussed elsewhere, paradoxes in explaining biological processes can be better understood by reviewing the principle of *causal identity* in the light of the *mesoscopic principles of causality* and *identity* that work in a synergic way in defining what biological units are relevant from an explanatory point of view and what relational properties should be considered in a first place (cf. Bertolaso 2013, Bertolaso in Greene 2017, Bizzarri et al. 2019). What this basically means is that any time we identify a correlation and make a causal inference we are *understanding by relating*, making a judgment about the dependencies and their regularities and recurrences among entities and facts. When dealing with complex systems and living entities and dynamics, this process takes the form of a *mesoscopic way of thinking* for which we define as explanatorily relevant those levels and interactions that maximize the correlations among dynamics and processes. What actually matter therefore are the relationships among the components of a system and how such interac-

tions reflect or emerge from the inter-level regulatory processes that are typically the object of inquiry in life sciences. This means that the dependencies we described in Sect. 1.2 have ontological foundations in the specific way living entities are constituted and maintained, and epistemic implications in the specific way we have to adopt them in order to understand them and manage with them in terms of prediction and control.

Let us now focus on the first aspect (ontological foundations in the specific way living entities are constituted and maintained) by looking at the kind of dependencies and dynamics that hold the integral functionality of the overall organic system. My discussion here relies on two papers that in my opinion very successfully show the relevance of this approach, beyond what I have already done in a previous volume (Bertolaso 2016) and that are already, in a way, present in the examples I offered above about cancer.

In Gorban et al. (2010), the focus is on the dynamics of correlation and variance in systems under the load of environmental factors, which is described as a universal effect in scenarios of crisis: “in crisis, typically, even before obvious symptoms of crisis appear, correlation increases, and, at the same time, variance (and volatility) increases too. This effect is supported by many experiments and observations of groups of humans, mice, trees, grassy plants, and on financial time series” for which a general approach is developed to explain the effect of individual and collective adaptation. Interestingly, the authors were able to analyze in different areas of practice (from physiology to economics, psychology, and engineering) the behavior of groups of similar systems adapting to similar environments. Groups of humans in hard living conditions, rats under poisoning, enterprises in recession, etc. show similar problems of diagnostics and prediction. Transversally, what the authors discuss is how “the correlations between individual systems are better indicators than the value of attributes. More specifically, in thousands of experiments it was shown that in crisis, typically, even before obvious symptoms of crisis appear, the correlations increase, and, at the same time,

the variance (volatility) increases too” (ibidem ...). This is represented in Fig. 1.2.

As Fig. 1.2 also shows, “[f]or some systems, it was demonstrated that after the crisis achieves its bottom, it can develop in two directions: recovering (both the correlations and the variance decrease) or fatal catastrophe (the correlations decrease, but the variance continues to increase).” The intriguing problem generated by this evidence is clarified when the authors consider not only the state but also the history of the systems. When ignoring the latter, the only difference between comfort and disadaptation is the value of variance: in the disadaptation state, the variance is larger and the correlations in both cases are low. Qualitatively, the typical behavior of an ensemble of similar systems, which are adapting to the same or a similar environment looks as follows: (a) “in a well-adapted state, the deviations of the systems’ state from the average value have relatively low correlations”; (b) “under increasing of the load of environmental factors some of the systems leave the low correlated comfort cloud and form a low-dimensional highly correlated group (an order parameter appears)” (ibidem).

As the authors correctly say, there is “no proof that this is the only scenario of the changes” although the appearance of an order parameter, in their studies, was supported by many experiments as well as by the destroying of the order parameter. However, what most interests us here is that there are similarities among apparently different systems and differences for the same system’s evolution depending on its history and under stress or in flourishing conditions that are well represented by the strength and number of the correlations.

Similar evidence was collected by colleagues of mine while looking at the effects of microgravity for cell population phenotypes. Physical factors, which are typically related to environmental conditions do matter, in space and time, in the transition processes of the populations (Po et al. 2019). Moreover, studies carried out on beta-cells equally show the relevance of dependencies among cells that are represented in this case by topological structures and functional correlations. Structure and functions are, as known, strictly related and therefore causally and explanatorily crucial in life sciences. This was also the focus of the project on the morphogenetic models

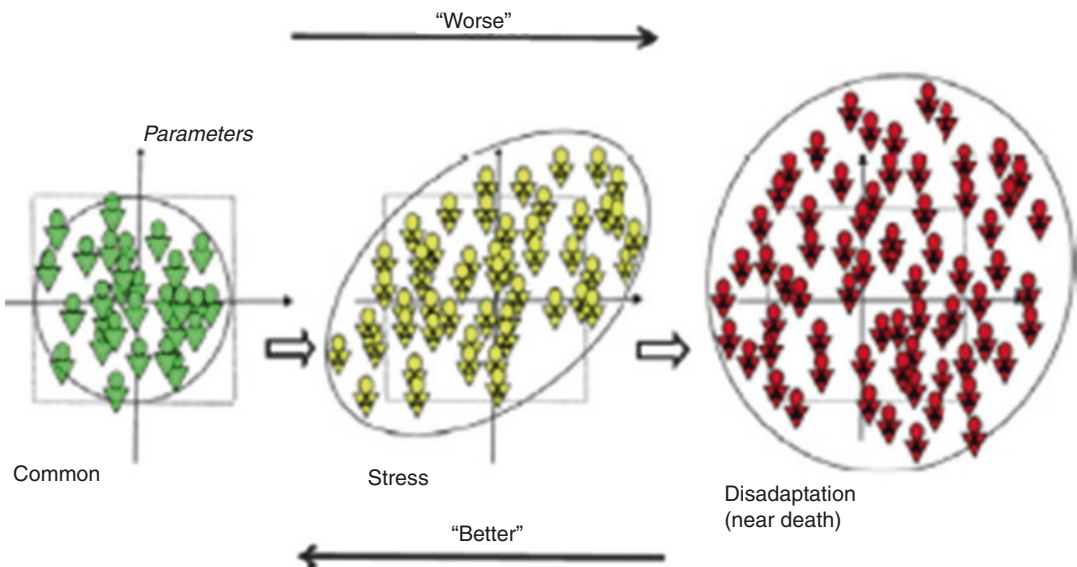


Fig. 1.2 Correlations and variance in crisis. Reproduced from Gorban et al. 2010. Ref. Complete for copyright request: Gorban AN, Smirnova EV, Tyukina T (2010)

Correlations, risk and crisis: From Physiology to Finance. Physica A Science Direct

already taken up by the mathematician René Thom (1975) who tried to give mathematical sense to the embryological concept of the morphogenetic field using the theory of topological transformations: “The fundamental problem of biology,” he claimed, “is a topological one, for topology is precisely the mathematical discipline dealing with the passage from the global to the local” (1975, p.151). For Thom, biochemical and genetic models failed to address the problem of morphological stability and form.

All these examples imply that what we are eventually pursuing in life sciences is careful *reconstruction of dynamics* and more specifically accounting for the (un)coupling of dynamics in space and time, which typically require an integral systemic approach. This also means that living beings should be understood from the point of view of their spatial-temporal ontology, of their *natural history* usually described in its two most fundamental components, i.e. their (biological) origin and context or environment.² Moreover, when we say that part of the ontological and epistemological challenge in life sciences consists precisely of combining the global and the local, the recurrence to a systemic viewpoint—or more widely a relational epistemology—does not merely mean taking into consideration interrelations. It asks for a deeper understanding of the *mutual dependencies* between what are considered the local and the global in a given system or model.

Complex systems are nonlinear systems characterized by a multiplicity of interacting components that give rise to higher-order, emergent phenomena. That is, the local behavior of small-scale components gives rise to a global behavior pattern, which in turn affects and restricts the local one. From galaxies to ant colonies—and to human societies—the science of complexity offers a new and computationally powerful lens for understanding the deep structures of nature, human societies, and human

minds (cfr. Bertolaso & Sterpetti 2020, Mervich 2020). But there is a specific way in which global patterns affect local behaviors and vice versa depending on the level of integration and dependence through which the specific system and entity is structured.

As Braun and Marom show (2015) in discussing behaviors of microorganisms, gene expression dynamics and neural systems organization, “regardless of the observed level of organization (protein, cell, network, or behavior), above lower boundaries that reflect fairly well understood physical constraints, observed and reported time scales are practically continuous.” That is, there is no time scale separation between processes occurring at different levels of organization. As the authors highlight, instead, such separation is possible and even a default assumption in the analysis of physical systems which allows coarse graining “lumping of many microscopic degrees of freedom to a small number of effective system variables. Where such separation does not exist, the path towards complexity is wide open” (ibidem p. 3. See also Bizzarri et al. 2019, Giuliani et al. 2014). As we will see more clearly in the next section, this fact is precisely related to the existence and explanatory relevance for organized complexities of what Weaver (1948) called a *middle region*. “The really important characteristic of the problems of this middle region, which science has as yet little explored or conquered, lies in the fact that these problems, as contrasted with the disorganized situations with which statistics can cope, show the essential feature of *organization*. In fact, one can refer to this group of problems as those of *organized complexity*” (Latin in the original, ibidem p. 4).

1.5 Hidden Simplicity in Biological Complexity

Let us now go back to the second point left opened in Sect. 1.2, that is, the epistemic implication of the dependencies we are focusing on. I said that the convergence between science and technology has been fostering the development of systemic approaches in order to take into

²This discussion has traditionally also taken the form of the nature-nurture debate that is however beyond the objective of this paper. For more details and reflections on this, see Bertolaso....

account dynamics that often emerge as networks of dynamic relations with elements that acquire a specific explanatory relevance depending on the level of discussion and the scientific question posed. Reaching such an understanding requires a system biology approach “that is defined as the science that deciphers how biological functions arise from interactions between components of living organism. It studies the gap between molecules and life” (Booger et al. 2007, p. 6). In Sect. 1.3, however, we have characterized such a gap as an ontological and epistemic feature of living entities that structure themselves through continuous coupling of dynamics that justify also the lack of time scale separability among such processes or dynamics. The global and the local imply each other in non-trivial terms and top-down causality holds as long as the question is precisely related to the dynamic stability that characterizes living entities’ behaviors, growth, and development in their most general, but also concrete, sense.

We can thus define a *mesoscopic level* as the scale of network organization at which functionality emerges in responses to higher-level system and environmental constraints (Bertolaso 2017) or the level at which “organizational principles act on the elementary biological units that will become altered, or constrained, by both their mutual interaction and the interaction with the surrounding environment. In this way and in this place is where general organization behavior emerges and where we expect to meet the elusive concept of complexity” (Bizzarri et al. 2011, p. 176, see also Bizzarri et al. 2019). Scientific, methodological, and philosophical questions regarding the adequateness/accountability of the models we develop to account for them rely upon this notion all the time, overcoming tensions generated by reductionist assumptions and making explicit the importance of a relational epistemology in life sciences. Its importance, in fact, lies not only in the identification of a level of the organizations that is successful in descriptive, explanatory, or even predictive terms of a phenomenon—which is already crucial for science and technological applications—but also in helping us understand the relevance of theoretical

terms and the abstraction from physical parts and elements of the concepts we usually adopt and apply to different fields of inquiry to describe dynamics and integrated processes. Consider, for example, the already mentioned concept of morphogenetic fields. Such a notion already implies logically and conceptually an explicit reference to inter-level dynamics that are realized in space and time. Similarly, when adopting the language of functional capabilities, instead of mere functions, we are emphasizing the possibility of biological activities to take place not only in time but also over time.

As shown in Fig. 1.3, a mesoscopic way of thinking is able to bridge observations and the identification of the system by making the relationships among the parts at a specific level of a biological organization a proper object of inquiry.

To give a final example of how these epistemic aspects contribute to a scientific question, I will briefly discuss empirical results related to the possibility of predicting Alzheimer’s on the metabolic basis of the areas of the brain.

1.5.1 A Case Study: Predicting Time-to-Event Development of Frank Alzheimer

I will follow methodological aspects of the case study as they well illustrate what I have theoretically addressed in the previous section and articulate how a comprehensive approach to predict time-to-event development of Frank Alzheimer’s can emerge adopting a mesoscopic way of thinking (Pagani et al. 2016; Pagani et al. 2017a, b). Assuming that the question was “how is it possible to find a parameter to predict time to event?” the expected impact would be a better estimation of the time before development of Alzheimer’s disease that can allow us to initiate therapeutic interventions (e.g. cognitive therapies) on time, to drastically improve patients’ quality of life.

To this end, the scientific problem was clarified in the following way. Brain metabolism (as measured by PET scan) is typically used in the pathology diagnosis of Alzheimer’s disease. However, the inherent complexity of the system

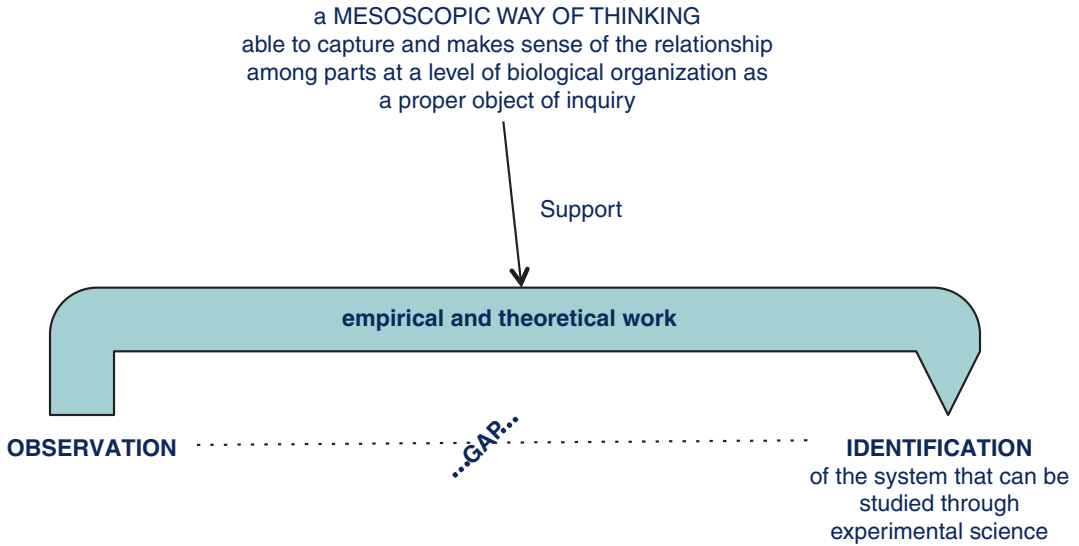


Fig. 1.3 The mesoscopic way of thinking

(brain) and its intermingled network of connections combined with the myriad confounding factors that impinge on the actual PET results make it very difficult to generate an efficient diagnostic criterium from PET data alone.

A reflection followed regarding the adopted strategy for diagnosis that brought it into a new perspective. The intermingled set of connections among brain areas could be switched from a curse to a blessing for diagnostic purposes and treatment: a global statistical measure of the average connectivity of brain metabolism is much more reliable than any single area-based PET Scan. Thus, by means of a classic statistical approach (principal component analysis) the authors measured the relation between the amount of variance explained by PC1 (the first principal component) and the disease severity (time elapsed before development of frank Alzheimer).

What the model offered emerged clearly at that point. The authors of the papers were able to measure the degree of coherence of brain metabolism in different patient groups. By doing so, we discovered that it was very well correlated with the time to development of disease (severity). We found that each brain area had its own specific dynamics in the process of detachment from the main connected component (when each single

area stops being coherent with the rest of the brain's metabolism). The finding allowed us to identify the most "promising areas" to develop an easy-to-use model for clinicians to perform diagnosis.

The reliability of the model, therefore, can be traced back to the theoretical assumption that the brain works as a whole as does its metabolism, which is a typical systemic assumption. For this reason, the model proposed works with two measures: the degree of order and the organization of the brain. These measures capture the essential aspect of Alzheimer's disease (from a phenomenological perspective), which is the breaking down of the brain's organization.

As a result of their findings, clinicians diagnosing patients at risk of Alzheimer's have begun working with the information generated by PET scans according to the new model and are making a clear contribution to the knowledge development, that is, that the strength of the mesoscopic methodology lies in this case in changing the correlation structure, thus providing a clearer framework for diagnosis and for brain metabolism research. The authors clarified a very important feature of brain metabolic organization: the decay of a single order parameter governing the entire brain metabolism occurs with a simultaneous increase in local organiza-

tions, where sub-clusters of brain areas detach from the “whole” and assume an autonomous local organization.

These findings were made possible by relying on two “complementary” tools: the PCA (principal component analysis) and the ICA (independent component analysis). The first tool captures the “global fields,” while the second focuses on “local fields.” The loss in the explanatory power of the global order parameter is strictly correlated with the rising explanatory power of local sets of correlations.

Neurologists and Gerontologists (Karolinska University Hospital, Stockholm, Sweden and IRCCS AOU San Martino-IST, Genoa, Italy) who asked for this contribution finally realized that the main mistake was how they framed the problem. What exactly was their (unresolved) problem? This was defined as whether or not it would be possible to predict the individual time-to-outcome (e.g. disease severity) of frank Alzheimer’s disease in patients presenting similar levels of impairment at the time of prediction, based on brain PET scan. Their contribution consisted therefore mainly in providing a different interpretation of PET results based on a mesoscopic (systemic) perspective. Clinicians contributed with data and medical expertise, and by selecting patients, based on their identification of the biological role and anatomical disposition of different brain areas, with same degree of cognitive impairment. They followed up on patients and provided treatment based on the mesoscopic model provided. But they also received a ready-to-use method to supplement clinical diagnosis based on cognitive examinations of PET (metabolic) scans that increased the accuracy of their diagnoses. The awareness about the methodological and epistemological potentialities of the mesoscopic approach therefore shows its potentialities in predictive terms as well.³

³Something similar is interestingly discussed in the paper by Where showing how the choice of coordinates is strictly related to the problem of invariance: “All indicators of the level of correlations are non-invariant with respect to transformations of coordinates. (...) Dynamics of variance also depends on nonlinear transformations of scales. (...) The observed effect depends on the choice of

Overcoming reductionist ontological and epistemological assumptions in scientific practice, in fact, opens up new possibilities of scientific and technological advancement.

1.6 Conclusions: A Relational Epistemology

This paper offers an innovative response that seeks to integrate the awareness of the above-mentioned challenges with the opportunities they offer to effectively advance biomedical and engineering sciences, through a relational epistemology to account for complex dynamics and living entities functional stability. Although I think that many of the issues discussed above are very closely related to the difficulty of comprehending a clear-cut notion of life and of living systems, the challenge of doing so opens the possibility of a pluralistic approach to describing and explaining them, that is, a richer understanding of their features and behaviors or dynamics. Thus, we can say that the difficulties associated with appreciating the plurality of models that can be developed to account for different aspects (*explananda*) of a living system and with developing a satisfactory explanatory model of inter-level regulatory dynamics when more or less strong dependencies (Fig. 1.1) are in place follow a wrong understanding of “reductions” and “complexity” within the practice and theories of life sciences.

As we have seen, there is a progressive collective orientation toward new and systemic epistemological assumptions and research practices throughout the scientific community at large. Conversely, as in some examples discussed above, a *multidimensional actionability* emerges and leads interesting future developments in life sciences highlighting, for example, the relevance of the spatio-temporal structures and how *fundamental elements* should be understood differ-

attributes. Nevertheless, many researchers observed it without a special choice of coordinate system. What does it mean? We can propose a hypothesis: the effect may be so strong that it is almost improbable to select a coordinate system where it vanishes”.

ently, and also (explanatory) *relevances*, i.e. what can be considered evidence of some biological phenotype or behavior. Data, in fact, are not self-evident, and little has been invested in research on data evaluation and validation processes as well as on their methodological assumptions. These facts have ethical relevance too if we consider ecological and biomedical scenarios in which right choices shape contemporary and future scenarios as for example in the case of epidemic. Therefore, providing solid data bases for modeling the behavior of living systems can generate an important value.

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A New Paradigm in Medicine: Psychoneuroendocrineimmunology and Science of Integrated Care

2

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Abstract

The industrialisation of medicine has produced the current biomedical paradigm in which health and disease dynamics, as well as individual characteristics would depend on elementary determinants: genes, microorganisms, structural alterations. Health, according to the reductionist paradigm view, would therefore be under the control of science and technique.

However, health and disease depend largely on the organisation of life, grounded by social organisation and individual behaviours. It is particularly evident in pandemic COVID-19 caused by SARS-CoV-2, a novel coronavirus zoonotic origin, that highlighted the serious difficulties and limitations of the pharmaco-

logical approach, highlighting the role of the public health service, the prevention and treatment at home and the integrated approach to the patient. The reductionist medical paradigm, pharmaco-centred, is insufficient to effectively combat the pandemic, which is tackled in the territory only with lockdown measures. A new model of care is also needed in the pandemic emergency.

Psychoneuroendocrineimmunology (PNEI) is the discipline that studies bidirectional relationships between psyche and biological systems. Within a single model, PNEI brings together knowledge acquired since the 1930s from endocrinology, immunology, psychology and neuroscience. With PNEI, a model is emerging of research and interpretation of health and disease, which sees the human body as a structured and interconnected unit, where the psychic and biological systems are mutually coordinated.

In an era of great danger, but also of considerable advancement opportunities, the scientific foundations of the new paradigm presented in this chapter are solid: they are the basis upon which it is necessary to construct a new science and a new care.

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2.1 Lessons from Pandemic Covid-19

The pandemic coronavirus disease 2019 (COVID-19) was caused by novel coronavirus, named 2019-nCoV, isolated for the first time in human airway epithelial cells by the Chinese Center for Disease Control and Prevention in late December 2019 in familiar cluster of viral pneumonia which was epidemiologically linked to a seafood market in Wuhan, Hubei province (Zhu et al. 2020). The novel coronavirus is the seventh member of the family of coronaviruses that infect humans and it was also named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) because of the genomic similarity with certain SARS-like coronavirus bat strains. SARS-coronavirus and MERS-coronavirus are two zoonotic coronavirus family members able to infect humans and cause severe and, in some cases, fatal disease, responsible for SARS and MERS outbreaks in Chinese province of Guangdong in 2002–2003 and in 2012 in the Middle East (Zhu et al. 2020).

The COVID-19 pandemic is escalating rapidly and spread in less than 2 months throughout the world. The World Health Organization (WHO) declared the outbreak to be a Public Health Emergency of International Concern on 30 January 2020 and the WHO Regional Director for Europe declared it as a pandemic on 12 March, 2020 (WHO 2020).

Is ongoing as we write an international race for the development of effective antiviral drugs and vaccines. However, within a few months, the SARS-CoV-2 has killed more than 100,000 people worldwide and thrown the world economy into an economic recession that promises to have unprecedented intensity.

The COVID-19 pandemic which, unlike SARS and MERS, was not limited to some eastern areas (China and the Middle East), affecting the heart of the West, has generated astonishment and disbelief among the population. In the imagination of the western citizen, epidemics were a reminder, mostly literary, of the past and, at the same time, a phenomenon of the most miserable areas of the world, which live without hygiene,

without food, without drugs. In this case, the epidemic is a dramatic reality in the wealthy, technological West, the cradle of scientific medicine. In addition, the infection usually has a banal onset, with moderate fever, cough, sore throat, asthenia, symptoms that everyone has experienced many times in life without serious consequences. And instead, in the pandemic context, the subject who experiences them can interpret them in a much more threatening way, like the beginning of a chain that, quite quickly, can lead to a condition of serious illness.

For these and other reasons, the new epidemic reality still finds it difficult to be mentally elaborated by the people on whom the restraining measures are incumbent, which, moreover, the governments of the western countries themselves have assumed with much reluctance and wavy attitudes.

Table 2.1 Comparison of old and new paradigm

Reductionist paradigm	PNEI paradigm
<ul style="list-style-type: none"> • Ignores the complex origin of diseases • Medicalises risk factors • Asymptomatic persons are redefined “ill” to facilitate the treatment with drugs • Failure of prevention • Supremacy of patentable therapies • Unsustainable costs in the face of poor results • Frequent medical errors • Low satisfaction of patients and physicians • Worsening of the disparities of access to care and health 	<ul style="list-style-type: none"> • Knows and cares for the human being in its entirety • Identifies the social and ecological determinants of health • Promotes the knowledge and self-awareness on which to base effective primary prevention policies • Orients molecular research within the systemic vision of the human being • Promotes effective integrated care and with a low impact on the human network and on the terrestrial systems • Promotes social solidarity and real equality of access to care and health • Promotes empathy between patients and health professionals

The concepts expressed in the left column are taken from: Fani Marvasti F, Stafford RS (2012) From sick care to health care—Reengineering prevention into the U.S. system, *New Engl J Med* 367(10): 889–891

The first investigations on the mental states during the lockdown among populations revealed a strong incidence of distress, anxiety, depression, sleep disturbances (Pfefferbaum and North 2020).

Similar phenomena are recorded among health professionals, especially the front-line doctors and nurses, who registered numerous deaths due to the infection contracted, in hospital and at home, in treating COVID-19 patients (Lai et al. 2020).

In the absence of effective drugs, the medical system can only offer emergency respiratory assistance, which is certainly a life-saving activity, but which is insufficient to effectively combat the pandemic, which is effectively tackled in the territory only with lockdown measures.

The majority of individuals who came into contact with SARS-CoV-2 exhibit few symptoms or often no symptoms. In a proportion of those infected, we now do not know exactly in what proportion, the infection can evolve into interstitial pneumonia which can give rise to acute respiratory distress syndrome (ARDS) and systemic inflammation, with possible fatal outcome. If we want to effectively tackle the pandemic, it is in the sea of the infected that we need to intervene with an integrated treatment program.

Clinically, in a first phase, fever, cough, dyspnoea, immune alterations occur, such as a high neutrophil: lymphocytes ratio, an overproduction of IL-1 β , IL-6 and, however, a low production of IFN- γ (Qin et al. 2020). If the disease evolves into a more severe form, other signs of systemic inflammation, particularly of the vessels, occur alongside these alterations: a condition produced by the so-called cytokine storm, that is, by the significant concentration of inflammatory cytokines released by immune cells and also from other damaged cells. The virus, in patients who develop more severe forms of the disease, evades the immune response that could block it and which is based on the cytotoxic Th1 and T lymphocytes. In place of this antiviral immune circuit, a hyperactivity of neutrophils intervenes. Neutrophilia and lymphopenia appear to be a constant trait of COVID-19. Neutrophil activity, if not accompanied by the action of B lympho-

cytes and cytotoxic T and T helper lymphocytes, not only does not eliminate the infection but can also be at the origin of hyper-inflammation, which characterises the transition to ARDS, with overproduction of inflammatory cytokines and extracellular traps of neutrophilic derivation (Neutrophil Extracellular Traps NET)(Van Avondt and Hartl 2018).

2.2 Support the Resilience of the Population

The great majority of the population has endogenous resources to counteract the infection which can be silent or with few symptoms. The psychoneuroendocrine-immunological (PNEI) approach, which studies the two-way relationships between the psychic dimension and biological systems in the environmental and social context (Bottaccioli and Bottaccioli 2020; Ader 2007), provides an adequate model for identifying risk factors and resistance to infection. It also illuminates the way to understand the effects of the infection on the overall health of the affected person, including his mental state (Bottaccioli et al. 2019).

As we described above, the balanced immune response to SARS-CoV-2 is central. A number of factors can regulate or unbalance the antiviral response, which are individual and collective. Individual factors related to nutrition, physical activity, stress and mental states. Collective factors related to state of environment and social conditions.

2.2.1 Environment

Recent research by the European Environment Agency has estimated that PM2.5 pollution in 2016 was responsible for approximately 412,000 premature deaths in Europe, caused by heart attacks, strokes and lung diseases (EEA 2019).

We have known for a long time that chronic exposure to air polluted by fine particulates, PM10, PM2.5 and ultrathin PM <0.1, coming from industrial exhausts, domestic heating and

vehicular traffic, can cause damage to the respiratory system. In particular, the PM_{2.5} particulate penetrates into the bronchial and pulmonary levels, while the ultrathin one can pass directly into the blood and spread to the organs.

Polluted air can contribute to the development of serious lung diseases, but also cause low-grade inflammation that favours the progression of the viral infection. Research in progress at Harvard University, Department of Biostatistics, School of Public Health, has recorded, in the USA, a direct relationship between exposure to air pollution from PM_{2.5} particulates and mortality from COVID-19. Harvard epidemiologists have found that the increase of only 1 $\mu\text{g}/\text{m}^3$ in PM_{2.5} is associated with a 15% increase in COVID-19 mortality rate (Wan et al. 2020).

In addition to pollution, the immune system is also affected by other factors, including nutrition, physical activity and psychological status.

2.2.2 Nutrition

A low protein diet is one of the main causes of immunodeficiency in the elderly population (Salazar et al. 2017) and the lack of an adequate amino acid pool has been associated with poor production of immunoglobulins, thymic atrophy, reduced proliferation of naïve and poor lymphocytes maturation of cells with lytic activity (Natural Killer, Lymphocytes with cytotoxic activity).

As is known, the food style selects and deeply shapes the microbiota, a complex set of resident microbial populations (bacteria, viruses, fungi) that form colonies in contact with the body's mucous membranes and therefore also in the respiratory mucosa. A state of dysbiosis, which can arise as a result of various conditions including the use of drugs (i.e. antibiotics, antacids), an inflammatory diet, surgery and hospitalisation, can be associated with various infectious and life-threatening clinical pictures. The clinical features of COVID-19 critically ill patients show widespread malnutrition.

The timely start of nutritional therapy is therefore vital, in particular in patients with organ failure and septic state, but it could significantly

change the disease process even in non-critical patients, hospitalised in ordinary wards or treated at home (Liang 2020).

2.2.3 Physical Activity

Reduced mobility is one of the main effects of forced pandemic quarantine. Although all sections of the population may be adversely affected by a prolonged period of almost total physical inactivity, the elderly population can once again pay the highest price. In fact, the reduced mobility in the elderly (Jiménez-Pavón et al. 2020) raises dangerously the fragility index upwards, rapidly depletes the muscle reserve and accelerates the bone turnover, promoting sarcopenia, osteo-articular degeneration, falls and osteoporotic fractures, worsens respiratory function by increasing the risk of acute seasonal diseases of the airways and exacerbations of chronic bronchopathies, alters the metabolism and the regulation of blood pressure, increasing the use of specific drugs and therefore health expenditure. Regular physical activity is also a trophic stimulus for the brain and immune system. Regular physical activity also modulates immune function, making the response against viruses and cancer cells (Th1 circuit) more efficient by counteracting immunosenescence (Abd El-Kader and Al-Shreef 2018) and age-related low-grade inflammation (inflammaging).

2.2.4 Stress

A condition of prolonged stress, such as during the COVID-19 pandemic, brings profound adaptive changes to the psycho-neuro-endocrine-immune network (Bottaccioli and Bottaccioli 2020): the psychological state is predominated by anxiety, depression, alteration of the sleep-wake rhythm and anhedonia; the biological side is characterised by impaired activation of the hypothalamic-pituitary-adrenal (HPA) axis and the release of circadian and stress-induced cortisol, imbalance of the autonomic nervous system and adrenergic hypertonicity, pathological