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Cover image: *Vegetation on the side of a rural road, Iowa, U.S.A., July 2021.* Photo courtesy of Stefano Serafini.

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Commentaries

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Programming Evolution: A Crack in Science

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Abstract

Nobel Prize winner, Jennifer Doudna, and Samuel Sternberg survey recent advances in a pioneering area of molecular biology. In an accessible and elegant style, the authors present the successes and challenges of a new DNA-modifying technique: CRISPR. They transmit their emotions of discovery, passion for research, and intellectual audacity. While greatly admiring the technical skills of the authors, who are among the best researchers in the field, this review critically stresses the limits of their experimental practices, namely: a vague or incomplete theoretical frame; often unreachable genetic targets; off-target effects; prior failures to deliver by other forms of genetic manipulation, and, finally, the intrinsic unpredictability of many phenotypic consequences of such a powerful technique. Due to these concerns, the authors' approach to organisms and Evolution is questioned with the purpose to generate an open debate.

Keywords: CRISPR, gene-editing, genocentrism, off-target effects, Evolution, theory of organisms

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Commentary on: Jennifer A. Doudna & Samuel H. Sternberg 2017, *A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution*. Boston, Ma: Houghton Mifflin Harcourt Publishers.

1. The Global Judgment: Vulgarization and Ethics

The book under review is a highly effective account of an extraordinary personal adventure in the invention and use of the latest genetic manipulation techniques. Despite having two authors, it was written in first person. This adds a personal touch to a highly readable style. In fact, one catches a glimpse into the passion of a selfless and very capable researcher immersed in a difficult world of biochemical techniques. One grasps moments of not only joyful success but also perplexing disappointment. In short, this book expresses a beautiful mind that is deeply dedicated to laboratory work. The author/narrator takes the reader, even an inexperienced one, by the hand on a difficult journey to "discover,"—or rather, invent the technical potential of biological mechanisms that are specific to the interaction between viruses and bacteria. This is then extended to the manipulation of DNA in eukaryotic cells. To this purpose, the book contains interesting information on viruses and bacteria, making it accessible to anyone. I will not further comment on the many fascinating details illustrated, for example, on how bacteria defend themselves from viruses, and how the chemical structures implied in this process can be reconstructed and used in the laboratories through insights and work.

The book also features the successes plus long lists of possible future applications of the manipulation made possible by the new DNA-editing techniques: "scientists

can now manipulate and rationally modify the genetic code that defines every species on the planet, including our own". Before discussing the proposed techno-scientific framework, let us move directly to the final part of the book. This addresses the ethical issues that relate to the potential of genetic manipulation in humans—especially the "improvement" of the species. Here, despite her enthusiasm for the techniques in which she contributed, the author stops short of the ethical challenge posed by such manipulations. With great humanity and intimate concern, the book presents the possible risks and abuses of such activities and proposes strict ethical limits to manipulations in humans. To this end, it leads us through the drama of the possible violence done to our species, and we can sense the peculiar sensitivity of a woman, the main author, faced with the manipulation of the embryonic genome of a future child.

2. Theoretical Problems

Having sincerely appreciated the book's merits in terms of writing, passion, and ethics, we now turn to a critique of its scientific content. Here, too, the authors' great intellectual honesty must be valued. Without hesitation, they take the Central Dogma of Molecular Biology (Crick 1958, p. 11) as a pillar of their theoretical framework. Today, this is often not the case. Even those who still and *de facto* base their work on it, especially in the laboratory practice of molecular biology, mostly refrain from mentioning it. If asked, they often present the Central Dogma as "a figure of speech" or a "simplification" of reality. Thus, we welcome a courageous and precise choice that does not leave us in vague, ill-defined theoretical frameworks. Of course, a problem arises: How is this dogma interpreted? Although not explicitly stated, there is no doubt that the book's interpretation refers to the harder version proposed by Watson in the 1960's. Such a version considers the DNA to contain the *complete* coding of genetic information, therefore, hereditary transmission. One cannot reproach the authors for a little vagueness in this respect since the notion of "(in-)completeness," which is clear and precise in mathematics, is unusual in the natural sciences. An exception was the 1935 seminal article by Einstein, Podolsky, and Rosen (known as the EPR paradox) which dealt with the "incompleteness" of quantum mechanics, providing a very rigorous and constructive critique of its foundations. Everything suggests that Doudna and Sternberg consistently consider DNA as *complete* in its prescriptive ontogenetic potential. Accordingly, the writing in the genes contains the complete set of instructions, it prescribes ontogenesis, and is at the core of phylogenesis.

However, a certain vagueness soon appears: the notions of "(genetic) information" and "program" are as ubiquitous as they are undefined. Since we are dealing with information encoded on discrete data bases (the chemical structure of DNA), we are led to believe that we are dealing with Shannon information (transmission) and/or Turing-Kolmogorov information (processing). As it is typical of biology, this lacks any precise reference to other notions of information. Let us not go into the diversity of the two notions here. For good reasons, these deal in a dual way with the relationship between the notions of entropy and complexity, therefore, of information that is usually seen as negentropy (Longo 2019). In fact, the lack of correlation between the "complexity" of an organism, however defined, and its DNA, does not seem to concern advocates of the genocentric approach. Although the authors consider DNA as a complete encoding of the organism, they recall that, for instance, the genome is hundreds of times larger in plants than in humans. Note that in 1999, the Director of the Human Genome Project, Francis Collins wrote that he expected to find 80,000 genes in man considering, not without pride, that the much less complex *C. elegans* (a microscopic worm of 1,000 cells) had 16,000 genes. Two years later, he recognized that there seemed to be 25,000 genes in man, or, as he later claimed along other authors, 21,000. The notion of a genetic program is even more vague. No attempt is made to identify the compiler, the interpreter, or the operating system. When an attempt was made by a few biologists using the most adequate language for string manipulation and term rewriting or "*term-editing*" (Church's lambda-calculus, which has been my specialty for long (Barendregt 1984; Kreisel 1982)), the use of recursion was still abusive (see Longo 2018; 2019 for a critique and sources). In sum, main stream molecular biology tends to fuzzily refer to precise notions such as information and program, while these notions are mathematically committed to a strong and specific form of "determination" (what and how determines what). This implicitly filters into views, experiments, and the interpretation of measurements.

This is rather inadequate for a text so rich in rigorous descriptions of viruses and bacteria, which aims at a global presentation, and calls for a clear definition of terms so liberally used in the discipline (including the foundational notion of gene).

In fact, what is a gene? In her book, *The Century of the Gene*, Evelyn Fox-Keller notes that our understanding of gene changed five times in the 20th century. In fact, the notion of gene is not defined in Doudna and Sternberg's book. However, the reader is lead to think that they consider it to be a segment of DNA to be associated not only with a protein but also a phenotype. This is at odds with their acknowledgement that some phenotypes are the result of a network of genetic expression, as it is the case for long-identified phenomena such as "alternative splicing" (Leff *et al.* 1986; see also Brett *et al.* 2001; Nilsen & Graveley 2010). These alternative initiations of transcription and translation (de Klerk & 't Hoen 2015) call for a revision of the "dogmatic" view of the correspondence of one mRNA to one protein in eukaryotes (Mouilleron *et al.* 2016). Such a further complexity goes beyond the concept of networks in the genotype-phenotype relationship (Brunet *et al.* 2018; 2020). A particularly telling example involves "overlapping genes." This phenomenon was discovered in the 1970's through the first-ever sequencing of a DNA genome (Barrell *et al.* 1976) and has been neglected since. Even now, some researchers (Schlub & Holmes 2020) consider it a typical feature of viruses, while many are starting to recognize it as a very relevant feature among the general category of "alternative proteins" in cellular organisms (Mouilleron *et al.* 2016; Brunet *et al.* 2018; Pavesi *et al.* 2018; Meydan *et al.* 2019). Overall, it is clear that these phenomena falsify the idea that genes are segments of DNA with a precise beginning and end, like software designed instructions. Indeed, the ENCODE project already highlighted "the complex patterns of dispersed regulation and pervasive transcription" and proposed to define a gene as "a union of genomic sequences encoding a coherent set of potentially overlapping functional products." Yet, the researchers involved are aware that their "definition sidesteps the complexities of regulation and transcription by removing the former altogether from the definition" (Gerstein *et al.* 2007).

In summary, the exact meaning of not only "information" and "program" but also "gene" is unclear. Oftentimes, the vagueness of these notions leave room for the attribution of extraordinary power to "genes." Everything is in the genetic information and elaborated by the genetic program. Both the program and the information are completely written in the genes. Of course, the authors point out that "in an individual, all the somatic cells have the same DNA." However, the contribution of the context in the control of gene expression is never referred to—perhaps because mentioning it would question the driving role of DNA in phenotype determination. Therefore, it is assumed that a very detailed program controls genetic expression in the DNA itself, from the zygote to the adult. This also means assuming that being human is written mostly in the 5,000 genes in excess of those of *C. elegans*, which causally contribute to each cell to take on very different forms and functions, from heart cells to, neurons and liver cells. The editing of this program would allow the organism to be completely steered in the ecosystem by the rational will of man, which is ethically acceptable and even necessary, according to the authors, at least in plants and animals.

A further theoretical gap in the book is the implicit use of another property that is essential to the proposed genocentric determinism: the exact stereo-specificity of macromolecular interactions and, therefore, of all the cascades from DNA to the proteins' functions to the phenotypes. Monod, in his 1970 book, Chance and Necessity, recognizes with great intellectual coherence that this property is "necessary for the transmission of information." Even more strongly, Monod claims that "the cell is a Cartesian mechanism," a clockwise chain of gears and pulleys. Macromolecular stereospecificity in a cell, as exact as the "Boolean algebras ... in our computers," says he, makes us understand how the processing and transmission of the genetic information contained in DNA may work. The first problem that arises from such a tenet is that physical chemistry has been treating interactions between macromolecules in a statistical way for long. Molecular interactions in a cell are no exception, as noted for genetic expression as early as 1983 by Kupiec (1983; 2010). Since then, the stochasticity of all steps of gene expression, from transcription to translation plus alternative splicing, has been extensively confirmed (see Elowitz 2002; Paldi 2003; Raj & Oudernardeen 2008; Waks *et al.* 2011 and more recently Boersma *et al.* 2019).

Generally speaking, macromolecular interactions are stochastic, they must be given in probabilities, and these

probabilities depend on the context. There are many references that justify this strong theoretical principle, but they are overlooked by the dominant genocentrism. In fact, the picture changes completely if one considers that, in this spirit, almost every "gene" is transcribed in *almost every* cell. Chelly *et al.* (1989) highlighted this long ago and this has been extensively confirmed since then: it is a matter of different probabilities (see also the references above on stochasticity). Moreover, twisting and pressing on chromatin changes the sites of DNA access, altering its expression (Cortini *et al.* 2016). This is certainly a crucial issue in embryogenesis, even though it hardly applies to computers. Similarly, many highlight "nongenetic cellular diversity" and "the role of regulatory network structure and molecular noise" (Balazsi *et al.* 2011). As stressed in (Braun 2015): "The genome does not determine the ordered cell state. Rather, it participates in this process by providing a set of constraints on the spectrum of regulatory modes, which are analogous to boundary conditions in physical dynamical systems." Clearly, this is a radical perspective shift from the genocentric approach: in this frame, the "boundary conditions" and their modifications, though still relevant for the dynamics, require a different kind of analysis. Typically, no single component of the dynamics has "completeness." Moreover, in physics, a difference in the boundary conditions may induce a difference in the dynamics or in its result. However, boundary conditions are analyzed differently from the "causes" of the dynamics itself. That is, these are clearly (mathematically) distinct from boundary conditions and are usually and beautifully framed in terms of conservation laws or symmetries, so that the notion of cause may be even avoided (a stone falls for *symmetry reasons* according to the theory of relativity).

In physics, though, the boundary conditions are supposed to be pre-set with respect to the intended process. In biology, instead, these "boundary conditions" are *co-constructed constraints*. They also depend on the constrained process that produces them: even the DNA, this fundamental, physico-chemical trace of history, undergoes a constant reconstruction. It is a massive *constraint* to the dynamics and the construction of macromolecules. It dynamically changes and differentially applies during ontogenesis, as well as, dramatically, in embryogenesis. More generally, the molecular, cellular, and organismal processes continually reconstruct membranes, microtubules, and other cellular components, as well as all the functional parts of the organism. These constitute constraints that contribute to the biological dynamics at all levels of organization. If so, they also affect the many macromolecular network that, though highly improbable from the point of view of physics, exist and work, but only in living cells, with a history. The original notion of a "closure of constraints" by Montévil & Mossio (2015) elegantly introduces the approach hinted here (see also (Deacon 2015)). Of course, modifying any of these constraints, especially one as important as DNA, leads to a change. However, this is because the change in the constraints turn out to re-channel the macromolecular processes, which, per se, are at least non-linear or, more generally, stochastic.

Of course, this analysis departs from Doudna and Sterner's determinism based on the genetic program, the Central Dogma, and the (unfortunately implicit) idea that macromolecular stereospecific interactions are exact. These theoretical assumptions are not simplifications for the sake of vulgarization. Rather, they are at the core of the book's perspective. These shaky foundation undermine the entire conceptual edifice of strict genocentrism, which has been presented to the reader as the only way of thinking. The different theoretical approach that we follow here, as proposed by many and discussed by Soto el al. (2016), offers another perspective when analyzing the evidence and the promises made in the book as for the role that CRISPR can play in "reprogramming" the living.

3. Theories versus Empirical Evidence

In science, as observed by Boltzmann, there is nothing more practical than a good theory. Can empirical evidence falsify the genocentric approach of the book? I think so, but this is not so obvious. Longo & Mossio (2020) present a close analogy between the genocentric view and the geocentric, Ptolemaic, perspective on the planetary system. In particular, the extraordinary progress in the knowledge of the skies due to the great Islamic astronomy and mathematics from the 8th to 14th centuries is acknowledged. The astronomers of Arabic language described all visible celestial bodies and their movements, especially the planetary system, from a geocentric perspective. No empirical evidence could falsify their account of the planets' movements since, mathematically, any finite number of points in

an ellipsis around the Sun can be interpolated by enough epicycles centered on the Earth. A change of perspective, actually, a metaphysical one, was required in order to consider the planets from the Sun's point of view. Only a dramatic change in theoretical principles could then falsify the geocentric perspective, such as the invention of the first fundamental conservation principle of physics, i.e., inertia, by Galileo. Then the "retrograde movements" of the planets, so closely described in Arabic, became totally impossible in the absence of masses in all the centers of epicycles, particularly after Newton's work. Note that inertia is a limit principle. It never applies in practice since visible movements are always constrained by gravitations and frictions. However, it allows us to understand all physical movements at once and analyze what constrains them: gravitations and frictions–since Galileo. In a sense, inertial movement is a "default" state of inert matter. Below, we will refer to a proper "default state" of living organisms, following Soto *et al.* (2016).

The relevance of the change of perspective and the invention of a "conservation principle" became clear when the new theoretical frame allowed for unifying falling apples and planetary movements (Newton, Hamilton), thus avoiding *ad hoc* descriptions and epicycles on top of epicycles. This recalls the *ad hoc* alphabetic writing in the zygote's DNA program that supposedly allows each cell to differentiate into a neuron or a leucocyte because genes control gene expressions, one on top of the other. In a context dominated by Monod, Jacob, and Lwof, the discovery of the epigenetic control of gene expression by Barbara McClintock has not been cited for 20 or more years (Fox-Keller 2003). Of course, some epicycles do exist, for example, the stationary satellites around the Moon or the satellites of planets with respect to the Sun.

In reference to the book under review, the authors further explain that the genes' alphabetic writing, with its complete control of ontogenesis, is "as editable as a simple piece of a text." Therefore, the fate of the embryo may be programmed at our rational will, at least for many traits. We can "imagine that the human genome is a large piece of software." As a reader of the book, I do understand the enthusiasm of a talented bio-chemist that suddenly sees, in the laboratory, the explosion of her combinatorial power over sequences of DNA bases. Yet, as a theoretician, I radically disagree with the loss of the sense of organismal life in a historical context that such a position transmits to the reader.

Is there empirical evidence confirming at least some actual achievements of the genocentric-programming perspective? Yes, and the authors provide long lists of results and much longer ones of future, potential applications. What is the problem then, at least with the results? Indeed, there are several.

First, like with the Islamic astronomers, some applications can work and may turn out to be very useful. We owe Ibn Yunus (Egypt, ca. 1000 A.D.) and many other great Islamic scientists for major advances in spherical trigonometry and the celestial observations that led to the Alfonsine Tables (Catholic Spain, 1483), which were successfully and widely used for navigation. However, generalizing their point of view and promises would be a major mistake, let alone their predictions entangled with astrology. Today, they are comparable to the ones in (Plomin 2019), where human behavior is also claimed to be written in a newborn's DNA.

Moreover, one should consider that observations and experiments in (molecular) biology suffer from the most severe irreproducibility crisis (Begley & Ionnidis 2014). As a matter of fact, biology is the theoretical place of diversity, variability, and historical specificity of organisms, which result from a phylo- and onto-genetic history. This means that one cannot (easily) generalize individual cases (or not in the same way as in physics, (Montévil, 2019)). As a discipline, molecular biology endures a high pressure to "publish or perish," which is disastrous for critical and time-intensive scientific insight and integrity (Longo 2014) and produces results with the shortest time validity (della Briotta *et al.* 2015).

Secondly, "measurement in biology is methodized by theory," as closely analyzed in (Montévil 2019). The fuzzy theoretical background of information and programming contributes to make results and data too often unreliable or uncertain when it comes to interpretation. Before Newton's theory, astronomers had experienced major problems with data on planets' Keplerian orbits whose irregularities were due to planetary gravitational interactions. Until Einstein's theory, measurements of the perihelion of Mercury were unintelligible. Data do not speak by themselves, even less very big sets of data, as they necessarily contain lots of spurious correlations (Calude & Longo 2017). As for our object of study, the "re-writing" of DNA may not only achieve its goal and modify the intended

phenotype but also scramble other parts of the DNA and thus affect the organism. There may be more than the expected changes induced by CRISPR in the DNA. Different genetic changes may be due to the diversity of nucleotide modifications in the target sequence, as well as a varying spectrum of sites that have been changed. Since unwanted effects could arise from both the target and off-target sites, the detection and measurement of unintentional or off-target changes may be much more difficult than that of changes at target sites. In fact, it turns out that this is the case (Chaudhari *et al.* 2020; Höijer *et al.* 2020, Modrzejewski *et al.* 2020) because the number and location of nucleotide changes are unknown, particularly if they occur with lower but non-zero probabilities in non-specific sites. Moreover, the changes may not depend on the nucleic acid sequence modified. Rather, they may depend on the scale of the induced modification (e.g. the level of the organism or the ecosystem), as well as on its (temporary or permanent) timing and duration (Adikusuma *et al.* 2018). Information theories of macromolecular exact editing of alphabetic codes do not allow to see these phenomena nor to interpret them.

Critical observations increase with time, including remarks on low efficiency of mutation repair, high rates of mosaicism, and the possibility of unintended editing outcomes that may have pathologic consequences (National Academies of Sciences, 2020; Alanis-Lobato *et al.* 2021 and references 10-14 therein). Recently, Leibowitz *et al.* (2021) have shown that "CRISPR–Cas9 editing generates structural defects of the nucleus, micronuclei and chromosome bridges, which initiate a mutational process called chromothripsis. Chromothripsis is an extensive chromosome rearrangement restricted to one or a few chromosomes that can cause human congenital disease and cancer. These results demonstrate that chromothripsis is a previously unappreciated on-target consequence of CRISPR–Cas9-generated DSBs."

We are far from the authors' claim of "the remarkable ability to rewrite the code of life with surgical precision and astonishing simplicity." Indeed, the techniques invented by the authors and their collaborators modify the DNA, can guide the production of a specific functional molecule, and induce, among others, a "gain-of-function" at the cellular level. However, their off-target or unappreciated on-target effects, and their entangled, non-compositional consequences over the different levels of an organism's organization—which are embedded in an ecosystem—are far from under control. We can heavily affect Evolution, not control it. In fact, we may succeed in modifying a few constraints to complex processes, but we never achieve the full control of them. We can act on nature, but cautiously. At least from now on, we should only do so based on robust practices and good theories—not vague, metaphorical conceptual frames for life.

In short, the CRISPR technology does modify the DNA, but where, and with what consequences over time? The belief that we can precisely cut macromolecular interactions is a delusion belonging to the myth of the cell as a "Cartesian mechanism" with computers and software replacing Descartes' clocks. Therefore, the key issue involves shifting from a genocentric perspective to a vision centered on the organism in its relation to the ecosystem, where the DNA represents a fundamental internal and historical constraint, in the sense of (Montévil & Mossio 2015). I believe and hope that the remarkable technical invention of CRISPR may be used in a sound way for knowledge and therapies, at least for rare monogenetic diseases. Most pathologies, however, even where DNA plays a key role, are due to the deformation of a wide network of gene expressions and molecular activities that interact within an organismal and ecosystemic context.

4. Previous Cases

The exuberant expectations of CRISPR has major precedents in the prevailing genocentric view. Revisiting a few of them may help in understanding the limits of today's promises. Based on my indirect personal experience, I will refer to cancer gene therapies. These have been expected for about a century and promised for at least 50 years as the age of the Somatic Mutation Theory of cancer (SMT). Such a frame refers to cancer as an entirely genetic problem and explicitly counts on CRISPR to solve it.

Since 1971, generously funded projects have heralded the final victory against cancer thanks to genetic therapies that can "reprogram" the "deprogrammed DNA." The former U.S. President Richard Nixon's "war on cancer" aimed to provide these therapies by 1976, the bicentenary of the American Revolution. By the year 2000, the major technological achievement of "decoding" the human genome was

seen as a further tool to solve the cancer puzzle and, once again, allow genetic therapies. Hanahan & Weinberg (2000), with over 20,000 quotations in a few years, and many other authors, promised genetic therapies for "eliminating suffering and death due to cancer by 2015," as the then Director of the National Cancer Institute, Andrew von Eschenbach (2003) put it. Indeed, within a few years, DNA analyses should have led to diagnosis and prognosis.

Many of us, unfortunately, have had a direct or indirect experience of this life threatening disease. Therefore, we know that in 2021 only the histologist at the light microscope can recognize if a cancer is primary, metastatic, benign, or malignant. Moreover, no plausible gene-based cancer therapy exists (see Baker 2014; Huang 2014; Maeda & Katami 2018). Eventually, Weinberg (2014), in a severe self-critique of his previous approach (see the 2000 paper above with Hanahan), acknowledges that "Genome sequencing also came of age and documented myriad mutations afflicting individual cancer cell genomes." Moreover, "63 to 69% of all somatic mutations [are] not detectable across every tumor region... Gene-expression signatures of good and poor prognosis were detected in different regions of the same tumor" (Gerlinger *et al.* 2012). "Sequencing has revealed that healthy cells in all tissues bear heavy mutational burdens and that mutations are not exceptional, but normal" (Mustjoki, Young 2021). Versteg (2015) also mentions tumors without mutations, while Gatenby (2017) observes that "cancer cells can display a seemingly paradoxical state in which their mutational burden is similar to and perhaps even lower than that of adjacent normal cells." On this basis, Gatenby hypothesizes that the tissue and the organismal environment drive the process, following (Sonnenschein & Soto 1999). Moreover, as Weinberg (2014) dares to admit, "most human carcinogens are actually not mutagenic." Forty years of contradictory analyses on asbestos (Huang *et al.* 2011), plus the aforementioned evidence, opened to the idea that, when the frequent and heavy mutational burden in cancer occurs, it is mostly a *consequence* rather than a cause of the disruption in cell control of reproduction (see also (Mally, Chipman 2002)). This phenomenon brings a specific diversity and leads to looking at cancer as a systemic problem (Bizzarri 2014; Baker 2021). Finally, in view of the mutational confusion in cancer, (Weinberg 2014) refers to it as "infinite complexity", thus some now bet on Big Data for machines to mend the human failure in understanding cancer's etiology. Unfortunately, mathematics shows that this is nonsense (Calude & Longo 2017; Montévil & Longo 2018). Despite the failure to deliver, too many—mostly avoiding any explicit reference to the central dogma or even denying its role in private conversations—continue to research or fund research *only* on cancer causing mutations, oncogenes, proto-oncogenes, or onco-suppressors (Kato *et al.* 2016; Rohan *et al.* 2018).

With a more robust organismal perspective, the Tissue Organization Field Theory (TOFT) (Sonnenschein & Soto 1999) allows us to understand why mutated cells from a cancer tissue may functionally normalize when transferred in a healthy tissue. For example, cells from a mammary neoplasm relocated in a healthy mammary gland stroma, functionally normalize (Maffini *et al.* 2005; Soto & Sonnenschein 2011). TOFT focuses on the failure of the triangular relation tissue/organism/environment in cancer formation. It also highlights the role of endocrine disruptors and other ecosystemic causes that affect the tissular and organismal control of somatic cell reproduction. Instead, the totalizing focus on DNA when studying and curing cancer keeps diverting attention and research from environmental causes, which are rarely mentioned by the tenants of the SMT. In this sense, the environment is not mentioned once in this book, despite about one hundred references to "cancer." As a matter of fact, the search for a genetic "magic bullet" has financially dominated for 50 years. This has largely excluded other research paths and minimized environmental analyses.

5. Remarks on the Method

Some may observe that I mentioned the frequent unreliability or irreproducibility of experimental results in the perspective I critique, while I attributed more validity to empirical evidence that aligns with my point of view. This depends on explicit theoretical analyses. Namely, I have stressed in several writings, often in collaboration with biologists, the inconsistency or incompleteness of genocentric determinism. These theoretical gaps result from vague or inconsistent notions of the gene, the information, and the program (see Longo 2019 for a synthesis on the misuse of "information" and "program"), as well as their implicit causality or determinism. Notwithstanding,

experiments are designed on the base of these vague or implicit notions and their strong consequences. These include the idea (deemed "necessary" by Monod 1970) of exact macromolecular interactions at the core of huge macromolecular networks. These networks would be designed like electronic circuits and would elaborate "Boolean algebras" (and this is even not meant to be "on average"). Such ideas are spread throughout molecular biology university textbooks and shape minds forever. This has led me to raise more a priori doubts on both the experiments and the measurements carried out in the information-genocentric framework. In fact, as stressed by Einstein in physics, theory decides the observables and the pertinent parameters. It proposes measurement tools and methods, as well as interpretations of data, as mentioned above in relation to the planets' orbits: vague or inconsistent theories undermine measurements, methods and interpretations.

Now, biology suffers even more from these biases because the historical and contextual specificity of organisms requires both diachronic and synchronic knowledge and measurement, as mentioned above—see also Longo 2017; Montévil 2019, and Montévil & Mossio 2020. Accordingly, a more explicit, well-defined, and robust theoretical frame justifies a greater reliance on empirical results. For example, despite branching into at least two different approaches (Gould 2002), Evolutionary Theories now make fantastic use of DNA fingerprints in paleontology. Oftentimes, this is done in mitochondrial DNA, which allows for reconstructing phylogenetic paths in theoretically well-construed perspectives. In the case of cancer, after 50 years of failed SMT-based promises of genetic therapies, TOFT has been explicitly based on Darwin's first principle (heredity as "descent with modification"), interpreted as a "default state" ("reproduction with variation") for all sufficiently fed organisms, and applied to somatic cells under massive differential constraints (constraining reproduction as well as motility in varying ways, according to the context). This seems more convincing than SMT principles, independently of the empirical failures of the latter. In fact, SMT implicitly refers to the Central Dogma and its set of biologically fuzzy notions of information and program. TOFT refers to Darwin and, today, to an increasingly robust theory of a "closure of constraints" in biology. Its theoretical frame no longer depends on Shannon's nor Turing, Church, and Gödel's information or programming theories (see Longo 2018 for a critique of the "Gödelitis" affecting some biologists). TOFT provides a relevant understanding of endocrine disruptors as carcinogens (Sweeney *et al.* 2015; Paulose *et al.* 2015) and prevention tools, thus opening to new therapeutic paradigms (Baker 2014; Bizzarri *et al.* 2014; Proietti *et al.* 2019), such as tumor reversion.

Second, I consider "negative results" particularly interesting in science since they have always opened the way to new paths of knowledge building (Longo 2018). At the theoretical level, randomness, in particular, is subtly related to undecidability, if understood as unpredictability in the intended theory (Calude & Longo 2016). If well defined, it thus provides a precise limit to knowledge. Now, the construction of undecidability is the "negative" result, which is the origin and pillar of the theory of computability or "elaboration of information" (Gödel, Church & Turing in the 1930's), so often cited in mainstream molecular biology. Of note is that in biology, randomness is not "noise" (Bravi & Longo 2015; Calude & Longo 2016). Rather, it is an essential component of the production of variability and diversity, and therefore, of the adaptivity and stability of organisms and ecosystems (a typical "information-theoretic" bug in biology is that it cannot distinguish randomness from noise–except by the notion of "incompressible sequence", a nonsense in biology). In other words, if one can "do something" or understand more through an insight into the limitations of knowledge, such as unpredictability (randomness), then I view this as a major theoretical advancement. Provable limits and constraints require precise definitions and structure theories and objects of knowledge. I Insist, the world-changing notions of programs and computation were defined in the 1930's to demonstrate incomputability. This involved clarifying the limits of knowledge and praxis instead of claiming the theoretical completeness of the analysis of this or that component concurring to a process. Such a method is thus fundamental in reinforcing the knowledge frame and in opening to new theories and applications. For these reasons, acknowledging the stochasticity of genetic expression and macromolecular interactions, channeled by biological constraints, is a convincing methodological pathway. Given the huge enthalpic oscillations of (not crystallized) macromolecules in a cell at a viable temperature, it is also empirically convincing. Yet it is also theoretically more robust than the vague

theories that envision the programmable genetic information to fully determine biological processes up to scattered noise.

This perspective shift suggests fundamental dualities. For example, the physical, highly improbable molecular networks in a cell do not completely determine bottom-up cellular activities and components. Rather, they are enabled by the very cellular constraints that they produce (Montévil & Mossio 2015). Indeed, there is no spontaneous generation from molecules to life, except for the totally unknown "singularity" at the origin of life. Existing and even artificial life is the result of a history, where each phylogenetic trajectory is triggered by rare events (Longo 2017). Accordingly, we better focus on how to understand and act on constraints, including the most fundamental one: DNA. This way, we can *canalize* processes by modifying constraints of various nature. In reference to the previous discussion, a typical example is "tumor reversion" (Bizzarri *et al.* 2014; Proietti *et al.* 2019; Kuchling *et al.* 2020; Sonnenschein & Soto 2020). Such a totally different approach contrasts decades of claims and failures about "rewriting tumor's scrambled genetic program." Furthermore, I think that this approach may shed a light also on our relationship with the ecosystem: we mostly acted and act on it by modifying constraints to its processes–with the effectiveness and the limits in understanding and prediction that are proper to this kind of actions.

As for theorizing, Weyl (1949) points out that the main methodological teaching of the theory of relativity, beginning with Galileo's relativity, is about moving from the "subjective-absolute" (so similar to the geocentric and genocentric approaches) to the "relative-objective" perspective. The construction of scientific objectivity requires analyzing the invariants, i.e. what is stable with respect to transformations of reference systems. In biology this should mean stability with respect to a "relativization" of levels of organization and scales, for integrating them. While considering DNA an amazingly important internal constraint to cellular dynamics, we must be able to move from the point of view of DNA to the organismal and ecosystemic perspectives and vice versa. Then, we must understand their integration and respective roles in the structure of biological determination (Noble *et al.* 2019).

As stated at the beginning of this note, I greatly appreciated the book for making some theoretical principles explicit. I also criticized it for leaving others implicit. Despite my admiration for the authors' experimental talent and insights, I wanted to express my disagreement with the framework of biological thinking they propose. Should Ibn Yunus (Egypt, ca. 1000 A.D.) be awarded the Nobel Prize for his contribution to astronomy? Definitely yes, despite the shortcomings of his theoretical vision. However, I think that now we should further investigate the practical and theoretical relevance of the analogue of Galileo's asymptotic principle of inertia in organismal biology, the default state of "reproduction with variation," an application of Darwin's first principle of Evolution, "descent with modification," which Darwin considered pervasive in all species (and that he discussed at length in four out of the first six chapters of *On the Origin of Species*). Note that somatic cells' "reproduction with variation" in a (healthy) tissue is a limit state, like inertial movement in physics. This is because reproduction in somatic cells is *always* (yet differently) constrained. By posing this Darwinian principle for all cells, including somatic cells, one follows in the footsteps of 150 years of microbiology and can better understand what constrains them within an organism, as well as the failure of these constraints in controlling cell reproduction, as it seems to mostly happen in the case of cancer (Soto & Sonnenschein 2011). This principle should combine with the unifying vision of organisms as a "closure of constraints," applied to all levels of organization. Both require scientists to specify the constraints of the largely brownian or chaotic molecular dynamics, as well as cells' reproduction and motility, i.e., their functional activities in an organism (Montévil & Mossio 2015; Soto *et al.* 2016; Bizzarri *et al.* 2020).

I believe that organismal biology will achieve further relevant results. The knowledge and techniques generated by the authors' and many others' work on CRISPR has contributed and may further contribute to this. A very interesting example has already been provided by fundamental studies, where "the CRISPR-based studies have surprisingly revealed that… effects on gene expression that are not mediated by the RNA transcript itself … occur in many loci that produce lncRNAs as well as in many loci that encode mRNAs" (Engreitz *et al.* 2016; Engreitz *et al.* 2019, p. 237). Following also the work in Cortini *et al.* (2016), Ramdas & Shivashankar (2015), and others, this confirms that the physico-chemical and context-dependent actions, including the structure of (long non-coding) lncRNAs,

may have a key regulating role, well beyond the genocentric informational approach. Understanding by both robust theories, instead of vague "metaphors", and by their experimental counterpart, while framing also the remarkable results obtained by the authors, should be an essential component of science, well before acting on nature.

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Feature

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Genetics and Epigenetics of Immortality from Bacteria to Humans

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Abstract

In humans the search for immortality became concretized by 6,000 B.C. leading to the building of large tombs and statues to immortalize the dead. This refusal to accept death is not limited to *Homo sapiens*. It occurs already in bacteria, extends to invertebrates and vertebrates, and includes even plants which avoid death by activating defense genes.

It turns out that consciousness is an obligatory prerequisite of death refusal. Experiments in single cell organisms (protozoa) revealed that a minimal memory of a previous attack was a prerequisite to initiate active defense. Already in plants consciousness is directly connected with the expectation of danger. They get advanced information from volatile compounds released from other plants that elicit their defense against insects. Consciousness is also not connected with larger brains, as disclosed by a comparison of the number of neurons in birds and apes.

Cloning is a natural form of ensuring immortality, which has been used by plants and animals before humans appeared on the planet. Cloning in humans was considered in the 1930s suggesting the cloning of Einstein. This procedure is not ethical and irrelevant. Besides such an individual would not have easily survived the harassment of the mass media.

More significant is that epigenetic effects disrupt and diminish the perpetuation of immortality by changing the genome. The evidence on epigenetics is now overwhelming extending from the simple eukaryotes (yeast) to plants and humans. RNAs have an important role in modifying gene function during development and they can even be incorporated into the genome creating novel gene constellations. Immortality is becoming more difficult to achieve than expected.

Keywords: immortality, consciousness, bacteria, plants, animals, humans, number of neurons, cloning of Einstein, epigenetics

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PART 1. The Search for Immortality

1. Definition of Immortality

Immortality is: "The indefinite continuation of the mental, spiritual, or physical existence of individual human beings" (Britannica Online Encyclopedia, Duignan, 2020).

1) The "indefinite continuation" is based on the concept of infinity, that has its origin as early as Babylonian astronomy, and which dominated most of the scientific thinking in physics and biology during the 1800s and early 1900s. The universe was considered to be infinite and the number of living organisms was also considered to be of enormous proportions.

2) It has a "physical existence" *i.e.* it is a palpable event in individuals. Every phenomenon is dynamic and here may lie a contradiction.

3) The concept is restricted to "human beings". This is also the view, characteristic of the Victorian Age, which asserted that humans were a species apart, with properties that were solely their attribute.

4) "Continuation of physical existence". This is a pivotal point. Present information, from genetics and epigenetics, reveals that the "continuation" is altered drastically during the physical transfer of gene information from generation to generation. Immortality is more restricted than it could be imagined.

Throughout the centuries, the concept changed, depending on the school of thought that dominated. The Dutch philosopher Spinoza (1632-77) refused to accept the immortality of individual persons.

Immortality has also been defined as "Exemption from death and annihilation" (Webster 1976). Here is introduced the concept of death which elucidates better this problem.

Actually, immortality, is like infinity, an abstraction of the mind. It is like our demand for perfect dice and parallel lines.

Immortality resurfaces in many ways, because it remains a deep desire of the human mind. It also turns out that immortality, consciousness and death are interlocked.

2. It Comes as a Surprise that Bacteria Already Refuse to Accept Death

With the discovery of antibiotics, such as penicillin, it was thought that infections would disappear as a result of the effective killing of bacteria. But that turned out not to be the case.

Antibiotic resistance in microorganisms became soon one of the main preoccupations of the medical profession. Following the widespread use of antibiotics, bacteria developed mechanisms that rendered them resistant to a large spectrum of medicines.

The genetic and molecular mechanisms involved became elucidated. In addition to its chromosome a bacterial cell produces *R* plasmids, small circular segments of DNA. These carry resistance genes which can be transferred between bacteria by: conjugation (transfer of DNA between two bacteria in physical contact) and transformation (the acquisition of new genes by the uptake of naked DNA). Once acquired, resistance genes are not easily lost and become spread in the population.

Multidrug resistance has been demonstrated in *Escherichia coli*, *Salmonella enterica*, *Staphylococcus aureus*, *Mycobacterium tuberculosis* and others (Dzidic *et al.* 2008).

3. Protozoa Also Refuse to Die

Protozoa are among the simplest organisms which possess a nucleus.

Trypanosoma brucei, which causes African sleeping sickness, counteracts effectively the chemicals used to combat it. The messenger RNAs produced from mitochondrial genes of this parasite undergo extensive RNA editing, which allows it to change its protein coat rapidly. By continuously producing new proteins it escapes immune attack and death (van der Ploeg 1990).

Minute cellular organisms actively refuse to remain passive when attacked by chemicals.

4. Millipedes Turn into Golf Balls when in Danger

Among the invertebrates are the small millipedes (Class Diplopoda) also known as thousand-leggers. There are more than 7,500 described species (Barnes 1980). The body consists of trunk segments which usually bear two pairs of legs. Calcium salts make the surface of these segments quite hard. Their movements invoke as many as 52 legs. When attacked by predators, the millipedes protect the vulnerable ventral surface by rolling-up the trunk into a sphere that protects also the head. They become as large golf balls. Sheldrake (2020) states that "A millipede coiled up, playing dead".

5. Faking Death in Spiders

Preston—Mafham (1996) describes in detail the various solutions that spiders discovered to avoid death and which "they play to perfection". They may: (1) fake death by becoming immobile, (2) move rapidly into a corner to hide, (3) fall down from the web carrying no thread, (4) they even disguise themselves as ants.

As Crompton (1950) wrote "Almost any animal will show fight when cornered".

6. Turtles when Attacked Turn Themselves into a Box

Turtles and tortoises have a body covered by rigid plates that protect their inner organs. At the same time these are so rigid and solidly connected, that they turn the carapace into an immobile shell. However, a number of turtles have evolved non-rigid shells with varying

degrees of movements found in American box turtles and Egyptian tortoises. These have acquired a hinge on the carapace which gives the animal the capacity to close the shell, with the vulnerable parts safely within, transforming the turtle into a tight box. This is a most efficient way to avoid predators (Halliday and Adler 2004).

7. Hedgehogs Roll-up with All the Spines Erect

The hedgehog is one of the oldest species of mammals. Molecular analysis suggests that by the end of the Miocene spiny hedgehogs had undergone radiation. At present they are classified into 16 species.

The number of spines in a hedgehog is about 7,000. Wilson and Mittermeier (2018) describe their behavior in detail: "When startled hedgehogs usually lower their head and body to the ground, which covers their tail and feet, and they erect their spines. If the threat escalates to physical contact, they roll-up by using muscles to draw down the spiny dorsal skin to envelope the whole body". "Spines become erect at opposing angles to form a dense barrier of protection. When a hedgehog is rolled-up, it presents a potential predator with nothing but a puzzling spiky surface. If necessary hedgehogs can remain rolled-up for hours".

8. Plants Are not Passive Organisms but Use Different Forms of Defense

Plants can respond to a wide array of volatile compounds released from organisms such as microbes, plants and insects.

Plant defense takes even the form of an anticipation of the predation by animals, such as insects, which eat their leaves or deposit their eggs on their tissues. They get advanced information from the volatile compounds released from other damaged plants which indicate the action of herbivores.

Priming of plant defenses against plant eating is not only mediated by plant volatiles. They also respond directly to the pheromones emitted by flies. The defense against egg deposition was studied in Scots pine (*Pinus sylvestris*) trees which were exposed to the sex pheromones of the sawfly (*Diprion pini*). The result was the differential expression of several defense-related pine genes (Bittner *et al.* 2019).

9. The Demand for Longevity Genes

The human craving for immortality takes more sophisticated forms. There is an eager demand for increased longevity.

Genetics has become an industry. The most advanced tools used in biotechnology, such as *CRISPR*/Cas and transgenesis are now employed to isolate and eliminate genes connected with disease, as well as to add genes with potential health benefits related to aging.

The discovery of long-lived genetic mutants has demonstrated that aging is a genetically regulated process. Single cell organisms (yeast), worms (*C. elegans*), insects (*Drosophila*), fishes (killifish) and the mouse, have been investigated. The experiments led to the isolation and sequencing of genes that modulate life span. Upon genome assembly 497 genes were identified which included those associated with longevity in humans. This work has been carried out by different research groups that also found genomic regions enriched for these genes (Lakhina and Murphy 2015).

10. Humans Concretize their Refusal to Accept Death

The human refusal to accept death did not become concretized in the earlier period of the transition of the great apes into hominids (6 million years ago). Even after the species Homo sapiens populated the planet there were no signs of death's refusal in an organized form.

The first burials, found below houses, appeared between 7,000 to 6,000 B.C. They reveal the way humans started to dispose of their dead indicating the first concern with immortality. In more recent times the deceased were equipped with objects and furnishings, to assist life in the afterworld.

Successively the living start to be represented in statuary and art, connected with their poitical power. The search for immortality became particularly well concretized in the large pyramids of Sudan and Egypt which are tombs. It also took extreme forms such as the terracotta replica of the entire army which was excavated at the site of the tomb of the Emperor of China (221 B.C.) (Scarre 2013).

Present day human societies create extensive cemeteries and these are filled, with elaborate tombs and statues of the dead, which in every way try to immortalize them.

11. Definition of Consciousness

In the *Encyclopedia Britannica* (2015, 2021) consciousness is described "As the perception of what passes in a man's own mind". The definition refers solely to human behavior, other living organisms are not even mentioned. But in an equally recent definition of consciousness Irwin (2020) emphasizes not only its "deep roots" but also its "broad distribution" across animal species.

12. Consciousness Extends to Most Living Organisms and is an Obligatory Prerequisite of Death Refusal

The evidence just described, on the refusal to accept death, discloses that several processes are involved.

1) Memory is an obligatory first component. When a *Paramecium* (Protozoa) bumps into an obstacle, it swims backward. If it gets a stimulus from the posterior end it swims more rapidly. Experiments using intracellular microelectrodes revealed that electrical charges and calcium concentration are involved in these responses. Another protozoa, *Stentor*, when mechanically disturbed, contracts the body with the aid of an internal system of microfilaments. Microelectrodes were also used in this experiment. Eckert and Randall (1978) concluded that these simple organisms had an elementary form of memory. An initial memory of an attack was a prerequisite to start active defense.

2) Griffin (1984) also pointed out that animals behave as though they expect a certain outcome at given times.

The fact that consciousness is directly connected with expectation is central. It means that organisms are aware that they must avoid a predator. Quite unexpected, but critical, is the finding that plants, are not only capable of reacting positively to danger, but also anticipate the event. They get advanced information from the volatile compounds released from other damaged plants. Their response even leads to the differential expression of several defense-related genes. The molecular memory of plant cells was also described by Baulcombe and Dean (2014).

3) The experiments in protozoans and plants demonstrate that living organisms, without possessing a brain or a nervous system, are capable of reacting positively to danger.

4) Several stages are an obligatory prerequisite to survival: (a) Repeated injury. (b) Memory based on the repetition. (c) Awareness of the event. (d) Response by modification of the genetic make-up (plants, bacteria). (e) Active defense against death.

Hence, without previous consciousness of an attack no active defense seems to be possible. Decision, which before was regarded solely as a human mental process, now emerges as a quality of the simplest cells, and it extends to complex organisms including humans.

13. Originally Consciousness Was Associated Solely with Large Brains but this Approach is Now Superseded

Sleep is a particular stage of consciousness. It has now become evident that "Sleep exists in animals without cephalized nervous system and can be influenced by non-neuronal signals, including those associated with metabolic rhythms" (Anafi *et al.* 2019).

Plants do not have neurons but can move, respond to their environment and show strong circadian rhythms. Many plants synthesize melatonin, a hormone secreted by the pineal gland which in lower vertebrates causes aggregation in pigment cells and in humans is connected with circadian rhythms. Also, animals that lack neurons altogether, such as sponges and *Tricoplax adherens* (Placozoan) have cells that secrete neuropeptides, which have direct synaptic effects and an indirect modulatory action on the nervous system. Hence, consciousness does not need to be solely dependent on the existence of a brain or even on the presence of neurons.

14. The Number of Neurons Increases with Organism Complexity

The idea that the brain was the sole source of mental activity, had its origin in the early finding that the human brain had billions of neurons. Besides, there is also an agreement, now well established, between an increase in neuron number and the increase in evolutionary complexity (Table 1).

However, an extensive study of bird and mammalian species, including apes, has revealed that the number of neurons is not the sole main factor in establishing high cognition.

Table 1: NUMBER OF NEURONS IN LIVING ORGANISMS.
Based on Polilov (2012), Olkowicz *et al.* (2016), Anafini *et al.* (2019) and Lima-de-Faria (2017, 2020).

ORGANISM	SYSTEMATIC CLASSIFICATION	NUMBER OF NEURONS	PROPERTIES
Sponges	Porifera	0	Synaptic scaffold proteins
Tricoplax adhaerens	Placozoan	0	Possibly neuropeptides
Many species	Plants	0	Synthesize melatonin. Strong circadian rhythms
Caenorhabditis elegans	Nematode worm	302	Time sleep. Lack circadian rhythms
Megaphragma mymaripenne	Insects wasp, animal with size of a protozoan	7,400	95% of neurons lose their nuclei
Drosophila	Insects Fruit fly	100,000	Circadian rhythms
Apis, sp.	Insects Bees	1 million	Nest building
Early vertebrates	Fishes, Amphibians Reptiles	Tens of millions	Nest building, Migration
From Goldcrest (songbird) to Cokatoo (parrot)	Birds	From 164 millions to 2,122 millions	Manufacture and use of tools, Migration
Most mammals	Mammals	Hundreds of millions	Nest building, Migration, Tools
Apes, Humans	Primates	Billions	Advanced tools

Table 2: NUMBER OF NEURONS IN BIRDS AND MAMMALS COMPARED TO TOTAL BRAIN MASS.
Based on data from Olkowicz *et al.* 2016.

BIRDS			MAMMALS		
SPECIES	NUMBER OF NEURONS	BRAIN MASS	SPECIES	NUMBER OF NEURONS	BRAIN MASS
Goldcrest *Regulus regulus*	164 million	0.36 g	Mouse *Mus musculus*	71 million	0.42 g
Starling *Sturnus vulgaris*	483 million	1.86 g	Rat *Rattus norvegicus*	200 million	1.80 g
Rook *Corvus fragilegus*	1,509 million	8.36 g	Marmoset *Mico melanurus*	636 million	7.87 g
Sulphur-crested Cokatoo *Cacatua galenta*	2,122 million	10.1 g	Galago *Galago* sp.	936 million	10.2 g

15. Birds' Cognitive Capacity Matches That of Apes

Birds have been found to have cognitive abilities that even surpass that of mammals. (1) Corvids (*e.g.* raven, rook) and parrots (*e.g.* macaw, cockatoo) appear to be cognitively superior to other birds, rivaling great apes in many psychological domains as demonstrated by numerous observations. (2) They manufacture and use tools. (3) Solve problems insightfully. (4) Recognize themselves in a mirror. (5) Plan for future needs. (6) Anticipate future behavior of humans and other species.

On a first inspection the architecture of the avian brain appears very different from that of mammals, but despite a lack of layered neocortex, large areas of the avian forebrain are homologous to mammalian cortex, conform to the same organizational principles, and play similar roles in higher cognitive functions. Avian brains seem to consist of small, tightly packed neurons (Olkowicz *et al.* 2016).

16. The Comparison of the Number of Neurons with Brain Mass Reveals that Birds Have Neural Densities Considerably Exceeding Those Found in Mammals

The cellular composition of the brains of 28 avian species was compared with that of several mammals including apes.

The brain of songbirds and parrots turned out to contain very large numbers of neurons, at neuronal densities far exceeding those found in mammals. Avian brains have higher packing densities than mammalian brains (Table 2).

These extra neurons are predominantly located in the forebrain. Parrots and corvids have the same or greater forebrain neuron counts, as monkeys with much larger brains. "Avian brains thus have the potential to provide much higher "cognitive power" per unit mass than do mammalian brains" (Olkowicz *et al.* 2016) (Table 3).

PART 2. Cloning is a Process which Existed Before Humans Arrived on the Planet

1. Definition of Cloning

"The term clone, coined by Herbert J. Webber, is derived from the ancient Greek word *klon*, "twig", referring to the process whereby a new plant can be created from a twig". And "Cloning is the process of producing individuals with identical or virtually identical DNA, either naturally or artificially. In nature, many organisms produce clones through asexual reproduction. Cloning in biotechnology refers to the process of creating clones of organisms or copies of cells or DNA fragments (molecular cloning)" (Wikipedia, edited 2020).

This definition includes statements that demand special comment.

1) Producing individuals with identical or virtually identical DNA. This is the critical component. Epigenetic results, described in the next pages, demonstrate that the identity is far from being fully maintained.

2) Cloning is a natural form of reproduction that has allowed life forms to spread for hundreds of millions of years. It is the reproduction method used by plants, fungi and bacteria.

Many horticultural plant cultivars are clones, having been derived from a single individual. Grapes represent clones that have been propagated by over two millennia. Other examples are potato, banana and tulips.

Many trees and shrubs form clonal colonies arising naturally when parts of an individual plant become detached and grow separately.

2. Plants and Animals Had Ensured Their Immortality

Asexual reproduction in animals occurs mainly in the early forms of evolution.

Hydras are Cnidarians which reproduce asexually by budding. A bud develops, as a simple evagination of the body wall, it forms tentacles and detaches from the parent becoming an independent hydra.

Regeneration is a phenomenon that leads also to immortality and which is difficult to distinguish from asexual reproduction.

Table 3: NUMBER OF NEURONS IN THE FOREBRAIN OF BIRDS AND CORTEX OF PRIMATES.
Based on data from Olkowicz *et al.* 2016. Note: The pallium is referred to as the cerebral cortex by some authors.

BIRDS **Corvids + Parrots** Forebrain			**MAMMALS** **Primates** Cortex		
SPECIES	**NUMBER OF NEURONS** pallial/cortical	**BRAIN MASS** (pallium)	**SPECIES**	**NUMBER OF NEURONS** pallial/cortical	**BRAIN MASS** (pallium)
Eurasian Jay *Garrulus glandarius*	529 millions	2.85 g	Owl Monkey *Cercopithecus hamlyni*	442 millions	10.62 g
Raven *Corvus corax*	1,204 millions	10.20 g	Capuchin monkey *Cebus* sp.	1,140 millions	39.18 g
Blue-and-yellow Macau *Anodorhynchus* sp.	1,917 millions	14.38 g	Macaque monkey *Macaca* sp.	1,710 millions	69.83 g

Regeneration has the particular property of starting in crystals (which have no genes), to expand in simple animals and in plants, but to slow down in higher vertebrates where only certain organs are likely to regenerate (Lima-de-Faria 2017, 2020).

Regeneration is due to memory at the cellular level because the original pattern is produced without external intervention. Initially in crystals it is a pure atomic process. In unicellular algae it is the release of chemicals that determines the pattern (Brachet 1974).

Flatworms (Planaria) have been an animal of choice in regeneration experiments. Any piece, about one tenth the size of an adult flatworm, will regenerate into a complete worm and the genes involved have been isolated. The Wnt3 genes induce a wave of proliferation, low levels of this gene expression cause head regeneration, whereas high levels of this ligand result in tail regeneration (Li *et al.* 2015).

In starfish and related echinoderms, 694 genes decide the ordered regrowth of organs (Purushothaman *et al.* 2015).

Plant regeneration is a general feature and takes many forms (Xu and Huang 2014). The pluripotency and totipotency of plant cells was demonstrated, as early as 1902, when a single somatic cell gave rise to a whole plant (Haberlandt 1902).

3. Cloning of Humans Was Considered Already in the 1930s

In the early days of genetics, the fly *Drosophila* was found to have giant chromosomes consisting of distinct bands which were considered to represent single genes or groups of genes. Band changes were found to result in natural mutations. P.H. Müller was an American geneticist who looked for a way to induce artificial mutations by using X-rays, demonstrating that new mutations could be produced at will by physical intervention.

At that time in Sweden, like in the USA, the United Kingdom and Germany, eugenics was not only a generally accepted procedure, but was imposed on people with lower social status. The aim was to improve the human "race" by carefully selecting parents.

Müller (who received the Nobel Prize in 1948) was also a supporter of eugenics. According to Rose and Rose (1999) he speculated on cloning Lenin and Einstein. Another geneticist, in England, J.B.S. Haldane, thought of cloning women as well. In the 1990s, and in later years, American novels and films have been based on this theme.

4. A Cloned Einstein Would Probably not Have Survived the Harrassment of the Media

The ethical implications of human cloning are extremely serious and at the same time irrelevant.

It is usually not recognized that a human being is born in a social and intellectual, as well as a historical environment that cannot be repeated. This environment is equally important, as the genetic constitution, in deciding his or her intellectual behavior.

Einstein was born in a period of revolutionary ferment that put in doubt all previous concepts, not only in science but also in society, due to the revolutionary works of Bakunin, Kropotkin, Marx, Lenin and others. Significant is that some of them lived in Switzerland like Einstein.

As Cahn (1960) describes in his biography, Albert Einstein was born in 1879 in Ulm, Bavaria, and moved later to Munich, Germany. There he was obliged to stand the intolerant and militaristic policy of Chancellor Bismarck. The result was that the family emigrated to a tolerant Switzerland.

As a child Albert was slow to talk and slower to read. In the German school he was in trouble since he refused to accept the dogmatic atmosphere imposed with "blood and iron". Important in his career was an elderly uncle who introduced him to the science of mathematics. In Switzerland he renounced his German status and became a citizen of Switzerland. Throughout his life, a violin and a sailing boat were among his sources of pleasure.

A cloned Einstein would lack all this familiar and intellectual environment. He would have no loving parents, no dedicated uncle and no land where all concepts in science and society were put into question.

A revolutionary mind, that transformed physics in its basic concepts, could only develop in a particular intellectual atmosphere.

The conclusion is inescapable. If Albert Einstein were to be cloned the new baby would have no parents, no family and no comparable society to

grow in. Moreover at once he would be declared a genius, a condition that he could not in any way satisfy. Suicide was most probably the only solution in sight.

It may be recalled that one of Pablo Picasso's children committed suicide since he was expected to be a genius like his father. Jaqueline, the wife of Picasso, also committed suicide. She could not stand the pressures of the mass media.

PART 3. Epigenetics Events Disrupt and Diminish the Perpetuation of Immortality

1. Epigenetics Was Established in the 1950s but is Heralded at Present as a New Discovery—An Example of How Science is Directed by Social Interests

It was the embryologist C. H. Waddington, who, as early as 1940, coined the term epigenetics (Rieger *et al.* 1968). By the 1960s he had created the Department of Epigenetics adjacent to the Institute of Animal Genetics at the University of Edinburgh, Waddington developed his novel concept in a series of books (1940, 1957 and 1962). But geneticists continued to refuse such an approach and even blocked the publication of the results.

In the meantime the active search for the cure of cancer and diabetes, became a pressing social issue. It demanded studies, at the molecular level, which finally led to the acceptance of epigenetics. However, as late as 2014, American cytologists called epigenetics "A New Kind of Inheritance" (Skinner 2014) transforming European science into an American discovery. This is an event that continues to occur quite often, discarding ethical principles.

2. Definition of Epigenetics

The term was originally defined as the branch of biology which deals with the causal analysis of development (Rieger *et al.* 1968). Later as "The study of the chemical modification of specific genes or gene-associated proteins of an organism.

Epigenetic modifications can define how the information in genes is expressed and used by cells." "Researchers have uncovered a range of possible chemical modifications to DNA and to proteins, called histones, that associate tightly with DNA in the nucleus. These modifications can determine when or even if a given gene is expressed in a cell or an organism" (Fridovich-Keil 2017, 2020).

3. Molecular Biology Confirms Epigenetic Events and their Inheritance

At present the evidence is overwhelming:

1. DNA sequences change during development. This is not only due to spontaneous mutations and numerous chromosome rearrangements but mainly to exon-intron shuffling (the process through which new genes are generated by recombination of one or more exons of other genes) which is a widespread event in the genome (Herbert and Rich 1999). Also the methylation of DNA sequences (addition of a simple methyl group to a nucleotide) can be transient but can be permanent, when set early in the development of the organism. This turns out to be the principal type of gene modification.
2. Another permanent modification of DNA is carried by histone acetylation and phosphorylation. Also certain modifications of this protein lead to expression or repression of genes in different kinds of cells.
3. DNA is not as important as we tend to think. The rigid order that directs embryonic formation is not directed by DNA but by microRNAs that before were considered irrelevant molecules. It is these small sequences, 21 to 22 nucleotides in length, that have the road map and which charter the events that lead to the production of a specific organism. These microRNAs are transcribed from non-coding genes (Carrington and Ambros 2003).
4. Some genetic modifications are spontaneously erased, when cells reproduce, thereby precluding their inheritance but other epigenetic modifications are heritable, being passed from parents to offspring, which is referred as epigenetic inheritance (Fridowich-Keil 2017).

4. RNAs Have an Important Role in Epigenetics and Can Be Incorporated into the Genome

As Lehninger (1975) stated "So far as we know, living organisms normally contain no functionless components, although there are some biomolecules whose functions are not yet understood". The molecular evidence gathered since then has vindicated the

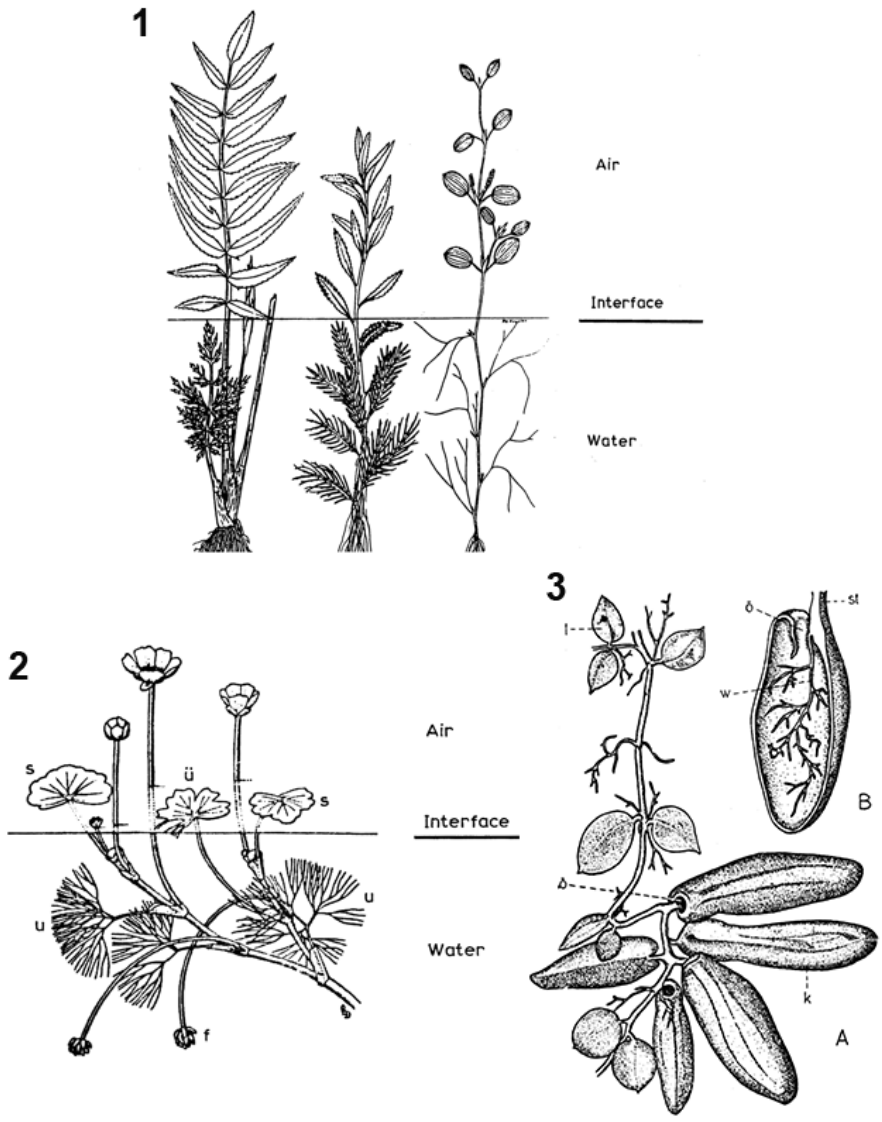
validity of his statement. The entire genome in living organisms generates a myriad of non-protein-coding RNA species that participate in gene expression and its regulation leading to epigenetic events. As Ponting *et al.* (2009) put it "Eukaryotic genomes are not the simple, well-ordered substrates of gene transcription, that was once believed".

As development unfolds most nucleotides in the genome are transcribed producing a huge array of RNA molecules differing in size, abundance and protein-coding capability.

Among these are the long noncoding RNAs (larger than 200 nucleotides) that are involved in transcription regulation.

Eukaryotes use relatively little of their genome to code for proteins. Besides messenger RNA transcripts are extensively processed, by alternative splicing and RNA editing, generating many different messages from the same gene.

Significant is that this RNA pool can be incorporated into the genome over time by reverse transcription (Herbert and Rich 1999).



Figures 1-3. Fig. 1: Three aquatic flowering plants showing different leaf patterns in air and water. **Fig. 2:** Three types of leaves are formed in *Ranunculus peltatus*: submerged with many linear segments (u), transitional form with a few linear segments (ü) and the floating palmate type. **Fig. 3: (a)** The carnivorous plant *Dischidia rafflesiana* has leaves with two different functions: normal leaves appear in the upper part and leaves in the form of a pitcher are formed in the lower part of the plant. The function of the upper leaves is mainly photosynthesis, whereas the lower pitchers attract insects and digest them. **(b)** Cross section of a pitcher.

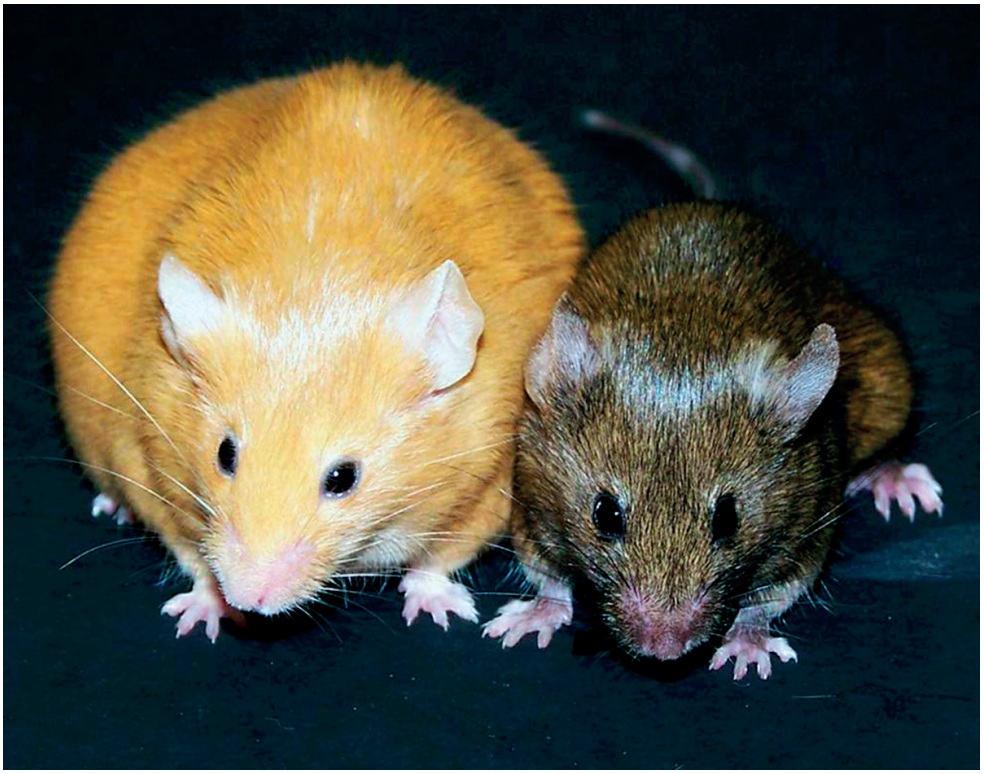


Figure 4: Agouti fat and yellow mouse (left), which functioned as a mother, at the side of its brown and skinny progeny (right). The mother received a diet rich in vitamin B12 and folic acid. This is a typical epigenetic effect since the agouti gene was switched off in the offspring which became brown.

5. Micro RNAs Affect Animal and Plant Development

Several hundreds of small RNAs and microRNAs, have been identified in animals and plants, which lead to the control of gene expression during development. The microRNAs arise from larger precursors that are transcribed from non-protein-coding genes. The precursors of these RNAs are termed *DICER* (in animals) and *DICER-LIKE 1* (in plants).

Plant microRNAs generally interact with their targets through near-perfect complementarity and direct messenger RNA target degradation. Short interfering RNAs (siRNAs) may also guide nuclear events including histone and DNA methylation, resulting in transcriptional silencing, a typical epigenetic event (Carrington and Ambros 2003).

In addition, RNA editing in plants alters the identity of nucleotides in RNA molecules, so that the information for a protein in the messenger RNA, differs from the prediction of the genomic DNA. In chloroplasts and mitochondria of flowering plants RNA editing changes C (cytidine) nucleotides to U (uridine) nucleotides. In ferns and mosses, it changes U to C.

In mitochondria there are approximately 500 editing sites and there are 40 editing sites in plastids of flowering plants (Takenaka *et al.* 2013).

6. Epigenetic Events Occur Already in the Simplest Eukaryotes

Escherichia coli (bacteria), *Saccharomyces cerevisiae* (yeast), *Caenorhabditis elegans* (worm), *Drosophila melanogaster* (fruit fly) and *Arabidopsis thaliana* (flowering plant) are the most investigated species from the genetic point of view.

Yeast is one of the simplest eukaryotic organisms and has been thoroughly investigated for decades. It turns out that it already displays epigenetic events (Allshire and Ekwall 2014). This is important because it shows that the phenomenon extends all the way from the simplest to the most complex living organisms (humans).

7. Epigenetics in Plants is a Widespread Phenomenon

The occurrence of different leaf patterns within the same individual plant has been described, and illustrated, for decades in botanical treatises.

Various species of aquatic plants, with shoots that are partly submerged under water and partly aerial, generally have submerged leaves that are highly dissected and thin in contrast with the thicker and entire, or only moderately lobed, aerial leaves (Figure 1). The different forms were attributed originally to environmental factors, such as

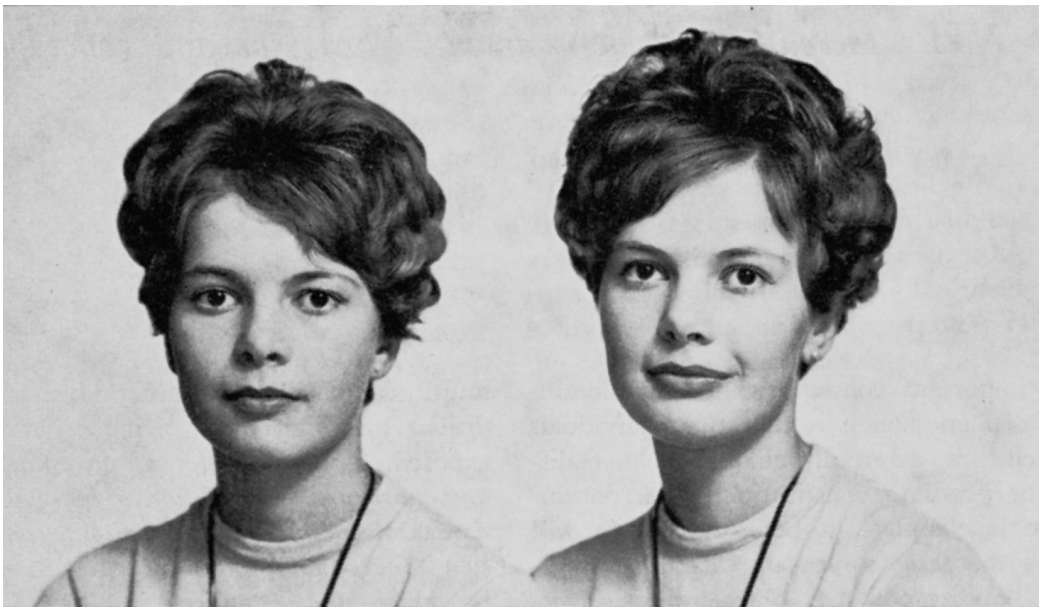


Figure 5: The identical twins Monica and Gerd. Monica is left-handed and has the hair to the right. Gerd is right-handed and has the hair to the left. They are mirror images of each other. Mutations in the gene Pitx2, in mice and humans, are involved in left-right symmetry.

temperature, light and humidity, but Greulach (1973) already pointed out that "environmental factors are of secondary importance" in bringing about this differences. Obviously, the environment has an effect but this remains to be investigated at the molecular level.

Another classical example is displayed by *Ranunculus peltatus*. Three different types of leaves occur in this partly aquatic species of flowering plants: (1) submerged leaves with many linear segments , (2) transitional forms with few linear segments and (3) floating leaves which are palmate (Figure 2).

Hedera (ivy) shows also two types of leaves. Experiments demonstrate clearly that it is an epigenetic phenomenon connected with gene imprinting. The juvenile leaves are lobed, but the mature leaves, that appear in the reproductive phase, are entire. Cuttings of the ivy from a flowering branch will produce only the entire pattern. The lobed form only reappears when the plant is propagated by seed, i.e, through sexual reproduction (Denffer *et al.* 1976). Cell memory and its erasing is now well documented at the cellular level (Gehring 1985).

8. In Carnivorous Plants Epigenetics Changes not Only Affects Structure but Also Function

Within the same plant, carnivorous leaves emerge at the side of non-carnivorous ones by change in gene expression. This epigenetic event is a general phenomenon in plants (Matzke *et al.* 2015) and is mainly due to RNA-directed methylation of DNA (Herbert 2004). Examples are: *Genlisia* has non-carnivorous flat green leaves above ground and distinct subterranean carnivorous leaves which form corkscrew traps. In *Triphyophyllum* three distinct types of leaves appear during development: (1) juvenile, non-carnivorous leaves, (2) carnivorous leaves and (3) mature stage with no carnivory but flowering. Two types of leaves occur in other genera: *Sarracenia*, *Nepenthes*, *Drosera*, *Pinguicula* and *Utricularia* (Figure 3). Not less than 8 genera of carnivorous plants produce leaves of different types within the same individual plant (McPherson 2010).

9. Mice Have Been the Animals of Choice in Studying Mammalian Epigenetics and its Relation to the Environment

Mice carrying the "Agouti" variant of a gene are genetically identical. However, depending on what their mother ate during pregnancy, the offspring can differ dramatically: they can be brown or skinny with the mutation switched off, or they can be fat, yellow, and prone to obesity and diabetes, when

the gene is on. The switch comes from the mother's environment which affects her genome and changes the fate of the offspring.

The pregnant yellow mother was fed a diet rich in nutrients such as folic acid and vitamin B12. The "Agouti" gene was switched off in the pups which are consequently brown and thin; not fat and yellow. This is considered a typical case of epigenetics (Figure 4) (Chong *et al.* 2007, Wolff *et al.* 2007).

Since then mice have been studied extensively to better define this type of inheritance at the molecular level showing that DNA methylation and histone acetylation are the cause of this process (Blewitt and Whitelaw 2013).

10. Genetic Similarities Between Mice and Humans

Mice became a model in many experiments performed to elucidate epigenetics in humans.

The "Mouse Genome Database" facilitated the comparison of mouse results as a model for human biology as well as disease (Eppig *et al.* 2015). It explored gene — phenotype — disease relationships between humans and the mouse but also microRNA interactions.

The two species are closely related not only anatomically and physiologically but their gene numbers and functions are also similar. In the mouse, the number of genes with protein functions are 24,613; of these 17,055 are mouse genes with human orthologs (i.e. homologous genes in different species that arose from a single gene in the last common ancestor of these species). The number of human diseases with one or more mouse models was found to be 1,323 which reveals their close relationship.

11. Epigenetics in Humans

Mice and rats have been used in the search for epigenetic events in humans (Morgan and Whitelaw 2008).

Genes termed *metastable epialleles* have been identified in the mouse which are responsible for color variegation. This is due to cells of the same type that do not express the gene. Examples of this phenomenon are *agouti viable yellow* and the *axin*-fused. Their epigenetic behavior is due to the insertion of a transposon silencing the promoter. DNA methylation at this promoter correlates with silencing. As mentioned above changes in the mother's diet during pregnancy alter the proportion of yellow mice within a litter. Methyl donors including betaine, methionine and folic acid result in a shift in the color of their offspring away from yellow and towards *agouti*.

In humans, a number of reports describe similar effects, and *metastable epialleles* were also identified, which are good candidates for transgenerational inheritance in this species.

Recent studies in humans, reveal that several diseases result from the disruption of the epigenetic state which can also be inherited across generations. These diseases are: decreased mental capacity, obesity and colorectal cancer in which aberrant methylation of DNA is involved (known as a main source of epigenetic modifications).

These mutations are difficult to establish in humans, but there is evidence that choline, which is an essential nutrient involved in epigenetic modulation of gene expression together with other methyl donors, has been found to have a role in carcinogenesis.

The result is that the US Food and Drug Administration, as well as similar European Authorities, recommended levels for adequate intake of choline (Zeisel 2017)

Psychiatric disorders, like drug and alcohol dependence, also conform with patterns of epigenetic changes (Wong *et al.* 2011).

For geneticists symmetries were considered a curiosity belonging to the domain of physics. For molecular biologists they continue to be of marginal significance since they cannot be explained by selection.

Müntzing (1961) published a figure of two Swedish twins Monica and Gerd. Monica was left-handed and had the forelock to the right. Gerd was right-handed and had the forelock to the left (Figure 5). He described them as mirror images of each other, but this change in symmetry, occurring within the same genetic constitution, was a problem foreign to the constancy of gene action.

Since then it has been found that: (1) Symmetries are a phenomenon that is inherent to matter, occurring already in elementary particles such as the neutrino. (2) Left-handed and right-handed structures occur in galaxies, carbon atoms, quartz crystals, amino acids, DNA configurations, flowers, snails and humans (Lima-de-Faria 1995). (3) Recently, the reversal of left-right forms in mice has been related to a mutation of a gene that controls embryonic polarity (Yokoyama *et al.* 1993). The homeotic genes are also involved in the

emergence of bilateral symmetry in the chicken, the mouse and humans (Yokouchi *et al.* 1991) and Ryan *et al.* (1998) found that the transcription factor *Pitx2*, which has a homologue in humans, also participates in left-right symmetry.

At present the patterns of Monica and Gerd indicate an epigenetic effect that resulted from mutations in genes directing embryonic development.

Conclusion

The evidence available at present on epigenetic effects, which extends from simple organisms, to plants and higher vertebrates (including humans), is overwhelming.

But we are far from knowing the main events participating in this process: (1) Knowledge is lacking of the own evolution of DNA as well as the type of mutations that result from this event. (2) Also the own evolution of RNA needs to be elucidated, since it is a major factor, due to RNA editing. (3) The molecular cascades that follow the alterations in DNA and RNA, are not known. (4) Neither are known the atoms which are responsible for deciding the final pattern.

These serious limitations on the atom behavior of simple and complex macromolecules are being elucidated by research carried out at the atomic level by the use of the large accelerators of electrons and neutrons which are now part of Lund University (Max IV and European Spallation Source) (Lima-de-Faria 2017, 2020).

Source of Figures

Figure 1. From Lima-de-Faria (1988), page 243. Originally from Greulach (1973).

Figure 2. From Lima-de-Faria (1988), page 245. Originally from Denffer *et al.* (1971).

Figure 3. From Lima-de-Faria (2017), page 37. Originally from Strasburger (1943).

Figure 4. From Wikipedia commons, File: Agouti Mice.jpg. 2021. CC by 3.0. Date 7 August, 2007. Source E-mailed by authors, Randy Jirtle and Dana Dolinoy.

Figure 5. From Müntzing (1961), page 54.

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Perspectives and Hypotheses

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Control of Cell Proliferation: Is the Default State of Cells Quiescence or Proliferation?

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Abstract

The control of cell proliferation in multicellular organisms remains a perennially controversial subject in experimental biology. In this essay, we examine the historical background and the rationale adopted by diverse theoretical and experimental research programs aimed at explaining *how* and *why* cells proliferate. We examine the premises that favor the notion that cells in multicellular organisms require direct stimulation from the outside (a task attributed to alleged growth factors) or from the inside (through the elusive action of oncogenes). Our analysis suggests that neither growth factors nor oncogenes directly stimulate the proliferation of cells. Based on evolutionary precedents, theoretical considerations and empirical data we posit instead that *proliferation* is the default state of all cells; thus, a search for extra- and intra-cellular inhibitory constraints promises to be productive when explaining this basic property of cells within the context of normal and abnormal developmental biology.

Keywords: proliferation, multicellular organisms, default state of cells, developmental biology

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Defining the Problem

From a historical and epistemological context, the biological sciences have evolved through two main basic theoretical foundations, namely, the cell theory and the theory of evolution. The cell theory posits that all organisms, be they unicellular or multicellular, are made up of cells and that multicellular organisms are generated from a single cell (Canguilhem 2008, Reynolds 2018). After overcoming criticisms regarding the place of syncytia and of individuality in the early 20th century, the cell theory remains unchallenged within the realm of biology at large (Harris 1999, Soto, Longo *et al.* 2016). Separately, Darwin's theory of evolution provided a coherent interpretation of how the many forms of life evolved (phylogenesis); it argues for common descent with modification and natural selection. Despite some course corrections to which Darwin's views have been subjected after the publication of the Origin of Species in 1859, such as the Modern and the Extended Evolutionary Syntheses, Darwin's contributions still remain as solid milestones in the history of evolutionary biology (Mayr 1982, Laland, Uller *et al.* 2014, Laland, Uller *et al.* 2015).

Notwithstanding these and other theoretical and empirical advances accomplished during the last century and a half, explanations regarding the control of cell proliferation in multicellular organisms remain controversial (Elsasser 1987, Noble 2012, Sánchez Alvarado and Yamanaka 2014, Longo, Montévil *et al.* 2015, Soto, Longo *et al.* 2016). For instance, a comprehensive explanation of how cell proliferation

is regulated in multicellular organisms and becomes integrated within the broader fields of cell, tissue and organ growth in size and shape is still lacking. In addition, epistemological and theoretical work aimed to resolve whether cell proliferation and motility are inducible or constitutive cell functions is still lacking as well. This essay will be dedicated to addressing these fundamental issues.

1. A Brief Historical Background

Toward the end of the second half of the 19th century, theoretical and empirical contributions by German pathologists solidified the role of cells in affecting healthy and diseased multicellular organisms while recognizing the interdependence of cells and the organisms to which they belong (Virchow 1960, Mayr 1982, Harris 1999, Sonnenschein & Soto 1999). This view was challenged at the beginning of the 20th century by three reductionist research currents. The first was the advent of genetics, which focused on the roles of genes in the phenotypes of organisms (Morgan 1910). The second was the introduction of cell/tissue culture into experimental biology as an important tool to study cell-based events (Willmer 1966, Sonnenschein & Soto 1999, Landecker 2007). Finally, the third current was the publication in 1914 of Theodor Boveri's book on carcinogenesis in which he posited that tumors were due to alterations in the structure of chromatin (considered by then to carry the genetic material) in a normal cell that would eventually become a cancer cell from which a tumor will grow in size and complexity by accruing mutated cells (Boveri 1914). Altogether, these three overlapping cell-based, bottom-up approaches (i.e., genetic determinism, cell culture and the somatic mutation theory of carcinogenesis) lead experimental biologists to adopt a cell-centered interpretative perspective of the living at large that became strengthened and hegemonic during the second half of the 20th century and which remains so to this day.

2. Is the Cellular Level of Biological Organization Alone Sufficient to Explain Morphogenesis?

From a single cell (the ovum), an adult multicellular organism evolves through a complex process. From early development to senescence, the process of organogenesis and its maintenance involves the interaction of different cell types within the many morphogenetic fields present in multicellular organisms. In most organs, those cell types are present in two distinct tissue types, i.e., the mesenchyme (which develops into adult connective tissue, a main component of the stroma, classically considered the support tissue of organs) and the parenchyma (classically considered as the functional, specialized part of organs). It is through those interactions that the shape and size of tissues, organs and systems are remodeled, repaired and regulated (Grobstein 1953, Howlett & Bissell 1993, Gilbert & Epel 2015, Cunha & Baskin 2016).

The reductionist turn alluded to above promoted the viewpoint that rigorous explanations of patterns of behavior happening at the tissue and/or organ levels of biological organization, such as proliferation, motility, and "differentiation", required a "mechanistic", bottom up, molecular description of processes happening within cells. In order to help in identifying the participants and their interactions during the processes of development, cell culture approaches appealed to researchers because they significantly reduce the number of variables present in animal-based experimentation. In the field of control of cell proliferation, cell culture offered the possibility of studying the cell cycle protagonists, their interactions and their dynamic properties while using hoped-for homogenous cell populations growing in glass or plastic culture dishes (Landecker 2007, Sánchez Alvarado & Yamanaka 2014, Pu, Han *et al.* 2020). Notwithstanding these intense efforts, an understanding of how cells control their reproduction remains undefined.

3. What do Cells do when Unconstrained?

Following the *Zeitgeist* established in textbooks and research publications on the subject, at the outset of our research program, ca. 1970, the consensus among researchers was that proliferative *quiescence* was the default state of metazoan cells (Bradshaw & Prentis 1987, Alberts, Bray *et al.* 1994). Consistent with this premise, in order to enter the cycle, cells would have required direct "stimulation" by either external (hormones and/or "growth factors") or internal factors

(oncogenes). Thus, despite accepting at the onset of our research program that *quiescence* was the default state of cells in multicellular organisms, empirical evidence we collected consistently contradicted it (Sonnenschein & Soto 1980). Specifically, the estrogen target cell lines we adopted as an experimental model proliferated in host animals only in the presence of estrogens, while in culture conditions they proliferated equally well regardless of the presence of ovarian hormones. After ruling out experimental errors, we still could not reconcile this paradox. To start with, we first wondered why biologists adopted proliferative *quiescence* as the default state for cells in multicellular organisms given that, in contraposition, microbiologists considered it axiomatic that the constitutive state of unicellular organisms was *proliferation* (see below). Altogether, after much empirical work, we concluded that *proliferation and motility* is the default state of all cells (Sonnenschein & Soto 1999, Soto, Longo *et al.* 2016, Sonnenschein & Soto 2020).

4. Searching for an Integrated Biological Context. A Theory of Organisms

Over the last decades, theoretical biologists expressed a need to complement Darwin's theory of evolution that addressed phylogeny with a theory that would explain ontogenesis (Polanyi 1968, Elsasser 1987, Woese 2004). This suggestion has received scant attention among biologists and thus, remained unfulfilled. Notwithstanding, theoretical foundations on the life cycle of organisms expanded and additional evidence accumulated in the field of control of cell proliferation. In collaboration with a group of colleagues in Paris, France, we identified three basic biological principles for a Theory of Organisms (Soto, Longo *et al.* 2016). Briefly, those principles are 1) the default state of proliferation with variation and motility (Soto, Longo *et al.* 2016), 2) the principle of variation, as the source of biological novelty and plasticity (Montévil, Mossio *et al.* 2016) and 3) the principle of organization, the source of robustness and stability (Mossio, Montévil *et al.* 2016, Montévil 2020).

In the current essay we are mostly focusing on the first of those principles, namely, the rationale behind our claim that the default state of *all* cells is *proliferation with variation and motility* (Soto, Longo *et al.* 2016). By virtue of being part of an interdependent system, during their lifetime, each cell in a multicellular organism is subject to a variety of exquisitely regulated controls that could either facilitate or prevent its proliferation. For instance, close structural contacts (among abutting cells) or interactions (through biochemical and/or biomechanical and bioelectrical forces) affect their proliferation and motility, as well as their metabolism, secretion and their overall phenotype (Sonnenschein & Soto 1999, Whited & Levin 2019).

5. The Control of the Proliferation of Individual Cells in Unicellular and Multicellular Organisms

Microbiologists who grew prokaryotic cells in a laboratory setting observed that in the presence of an adequate supply of nutrients, bacteria (prokaryotes) placed within permissive ranges of temperature, atmospheric pressure and pH, proliferated constitutively and exponentially (Luria 1975, Sonnenschein & Soto 1999). Later on, comparable patterns of *proliferation* were found when studying unicellular eukaryotes. Hence, among microbiologists, it became axiomatic that proliferation is a constitutive property of unicellular organisms; this constitutes their default state. This property not only applied to the microorganisms propagated in laboratories but, by extension, it also applied to the hypothetical first common ancestor of all living organisms, as well as all of its descendants. Arguments consistent with such views were already made by Malthus by the end of the 18th century (Malthus 1798), and later by Charles Darwin who, influenced by Malthus' views, inferentially strengthened the notion that *proliferation* was the default state of cells as documented by a passage in "The Origin of Species", namely "There is no exception to the rule that every organic being naturally increases at so high a rate, that, if not destroyed, the earth would soon be covered by the progeny of a single pair" (Darwin 1864). For the purpose of the current analysis, it then becomes relevant to ask... *Has the axiomatic default state of unicellular organisms remained unaltered through the advent of multicellularity to the present day?* So far, we have found neither theoretical nor empirical evidence that would challenge this axiom originally adopted by microbiologists (Sonnenschein & Soto 1999).

5.1. The Literal Adoption of Operational Terms: the Reification of Growth Factors

The success of microbiologists in culturing bacteria in a laboratory setting motivated other biologists to address comparable basic questions while using, instead, more complex, multicellular organisms. They found, unlike bacteria, that cells from metazoa required a more complex propagation medium containing macromolecules, like those present in serum, embryo extracts, etc. Even today, after considerable investments in designing so-called chemically-defined media, only a few cell lines can be routinely propagated in them. Components of those supplements were considered stimulators of cell proliferation, that is, the equivalents of "growth factors". Later, operationally defined "growth factors" were inferentially assumed to be real entities that indeed induced cell proliferation. Under this scenario, it was implicitly assumed that the default state of cells in metazoa was *quiescence* and that serum contained specific molecules (stimulatory signals) that stimulated (induced) cell proliferation. The term "growth factors" then acquired a narrow, regulatory meaning.

Starting in the 1950s, experimentalists began searching in earnest for stimulators of cell proliferation. Rita Levi-Montalcini, a biologist, and Stanley Cohen, a biochemist, were the first who characterized what eventually became known as a nerve growth factor (NGF) and an alleged epithelial growth factor (EGF), respectively. Levi-Montalcini, for her part, signaled all along that NGF did not stimulate the proliferation of nerve cells, but affected, instead, the number of neuron dendrites (Montalcini 1986). In contrast, Cohen and his followers insisted on claiming that EGF indeed stimulated the proliferation of cells (curiously, EGF mostly affected fibroblasts). Pragmatically, however, Cohen and his followers reached this conclusion when interpreting data showing an increased tritiated thymidine incorporation by cells in culture conditions, a method that falls short of actually measuring an increase in cell numbers (Carpenter & Cohen 1976, Cohen 1986, Sonnenschein & Soto 1999).

The rationale for claiming that "growth factors" could stimulate cell proliferation was curious. In a strategic reversal, the alleged physiological roles of "growth factors" in the whole intact animal were investigated after they were first purified. That is, instead of being discovered in the process of explaining a physiological function, like what happened with the discovery of insulin or estrogens, the strategy to discover "growth factors" consisted first in purifying a polypeptide from either serum, organ extracts or other complex natural sources and subsequently asking whether the suspected growth factor had indeed a physiological proliferative role when tested in culture conditions or administered to animals. For example, EGF was found, serendipitously according to both Cohen (Cohen 2008) and Gospodarowicz and Moran, in extracts of salivary glands of male mice during the purification of NGF (Gospodarowicz & Moran 1976). When these preparations were injected into newborn mice, they accelerated eye opening and tooth eruption. Intriguingly, both phenomena are related to epithelial cell death, rather than cell proliferation. Paradoxically, the cell line A-431, which was used to characterize EGF receptors, responds to EGF exposure by inhibiting cell proliferation (Barnes 1982).

Relevant references have shed both light and confusion on the subject. In the late 1970s, as an increasing number of novel alleged growth factors began to be described, Gospodarowicz and Moran listed a number of basic requirements that would have validated their presence (Gospodarowicz & Moran 1976). The requirements to qualify for becoming legitimate growth factors were 1) to initiate DNA synthesis; 2) to initiate one cycle of division in confluent cultures; 3) to trigger several cycles of division in sparse as well as confluent cultures; and 4) to generate clonal growth (starting from a single cell to a monolayer). Crucially, the specific evidence collected in culture conditions should have been matched by a comparable physiological proliferative role in animals. Other than the first of those requirements, i.e., to initiate DNA synthesis, the others remained unfulfilled. When one tests the function of a polypeptide, the control should not be the solvent, but instead should be a scrambled polypeptide containing the same amino acids with a random sequence. Additional objections could be raised. For instance, within a homeostatic context, nutrient starvation is not a valid alternative to evaluate the control of cell proliferation in a live animal. For instance, starved cells could have been taking up the polypeptides (EGF and others) added to the basic nutritive medium as welcomed supplemental nutrients needed to synthesize some DNA, but not enough to complete the final cell cycle

steps that Gospodarowicz and Moran alluded to as being required to fulfill their original growth factor definition. Also, proliferation rates in culture conditions in which those alleged growth factors were tested were either not exponential or showed no significant differences in cell proliferation rates (Carpenter & Cohen 1976, 1987). These inconsistencies between data on cells in culture conditions and physiological roles of alleged growth factors were noticed at the time by Renato Baserga, an experienced cell biologist, who nodded cautiously, "... this is not to say that reproduction *in vivo* is regulated by the same factors, but cell cultures are where we must start" (Baserga 1985).

Additional objections to the notion that the alleged growth factors directly stimulated cell proliferation were raised by others. For instance, EGF and TGF-alpha primarily stimulated cell spreading which, in turn, may have indirectly affected cell proliferation (Barrandon & Green 1987). Finally, toward the last decades of the 20th century, the advent of powerful recombinant DNA technology allowed for the use of species-specific recombinant polypeptides, and the generation of mice carrying null mutations (knockouts) of putative growth factors and their specific receptors. In the words of Durum and Muegge, the introduction of this technology provided the desired "acid test for the function of a gene" and consequently, claims emanating from data gathered in culture could be reliably tested (Durum & Muegge 1998). The data collected, however, failed to show that those alleged growth factors singly or in combination had a direct role in the control of cell proliferation (Miettinen, Berger *et al.* 1995, Sibilia & Wagner 1995, Threadgill, Dlugosz *et al.* 1995, Guo, Degenstein *et al.* 1996). Reports concluded, instead, that these alleged growth factors were either i) "survival factors", or cell death inhibitors (Koury & Bondurant 1988, Williams, Smith *et al.* 1990), ii) made cells spread (Barrandon and Green 1987), or iii) affected cell differentiation that was unrelated to the control of cell proliferation. These alternative conclusions to those reached by Stanley Cohen and his followers fit well within views that once cells are placed in an environment where nutrients are in adequate supply, in the absence of *bona fide* inhibitors, they exercise their constitutive ability to proliferate making stimulation moot (Sonnenschein & Soto 1999).

A clarification is in order: the data stemming from work in developmental biology suggest that these polypeptide alleged growth factors may indeed play roles as morphogens (Gilbert 2013). In this essay dedicated to defining *the how* and *the why* in the control of cell proliferation, however, we are merely challenging the notion that these polypeptides have instructive properties for cells to enter the cell cycle in living organisms. The answer is that they do not (Cohen 1965, pp. 251-272, Gospodarowicz & Moran 1976, Cohen 1986).

Equally baffling have been claims of endogenous stimulators of cell proliferation (oncogenes) by proponents of the somatic mutation theory of carcinogenesis (Huebner & Todaro 1969, Tabin, Bradley *et al.* 1982, Bishop 1991, Varmus & Weinberg 1992, Malumbres & Barbacid 2009). In fact, an extended volume reportedly aimed at reaching a consensus about the stimulatory role of growth factors and oncogenes on cell proliferation dealt, instead, with intracellular biochemical interactions triggered by so-called growth factors and oncogenes rather than with verifying the biological role (increased cell numbers) of those extra- and intracellular alleged stimulators of cell proliferation (Bradshaw & Prentis 1987). A comparable conflation between the notion of control of cell proliferation and activation of signal transduction is still observed in current publications (Lavoie, Gagnon *et al.* 2020). Meanwhile, contemporaneously published textbooks and research articles retain the notion that *quiescence* is the default state of cells in multicellular organisms and that growth factors and oncogenes directly stimulate the proliferation of cells (Alberts, Johnson *et al.* 2008, Weinberg 2014).

6. The Why and the How of Cell Proliferation in Multicellular Organisms

During the diverse stages of development, some cell types proliferate while others do not, regardless of their location in the organism and their differentiated function. Instead, when placed in culture conditions, explants originating in cell populations that are mostly dormant in animals proliferate robustly (for instance, fibroblasts) (Hayflick 1992). In the early 20th century, this cell behavior was interpreted as equivalent to having been "des-inhibited" from a proliferative inhibition exerted while inside multicellular organisms (Carrel 1912). By adopting the premise that, under

homeostatic conditions, proliferation and motility is the default state of all cells, it becomes implicit that a cell's metabolic or secretory activity and its phenotypic changes appear to be not relevant when answering the question, *why* do cells proliferate?

6.1. How do Cells Proliferate?

"Established" cell lines have been extensively used for the study of the phases of the cell cycle; they better tolerate nutrient starvation, metabolic poisoning, extreme environmental temperatures, or exposure to undue physical stress. Under these experimental conditions, cells in culture can be prevented from proceeding with the cycle stages. Meanwhile, as alluded to above, molecular interactions taking place along the cell cycle phases can be explored in order to answer the question, *how* do cells proliferate? In fact, other than those estrogen and androgen target cells that we worked with there is a severe paucity of "physiological" means of synchronizing cell populations growing in culture conditions. To remedy this shortcoming, experimentalists had adopted non-physiological methodologies (e.g., nutrient starvation, poisons, etc.) in order to synchronize cell populations. This has been the preferred strategy to define the successive steps and pathways that cells take in order to generate two daughter cells from the metaphoric mother one (Min, Rong *et al.* 2020). Indeed, by 1990, Paul Nurse, who used both unicellular eukaryotes (yeast) and cells from multicellular organisms already concluded that "...A case can now be made for the existence of a universal control mechanism common to all eukaryotic cells" (Nurse 1990). In this context, answers to the *how* question became linked to the role played during the cell cycle by enzymes, cyclins, transcription factors and other components present in and within the cell's plasma membrane.

Soon after Nurse made this generalization, this field of research exploded with descriptions of the myriads of biochemical interactions occurring during the phases of the cell cycle of all types of eukaryotic cells. Dozens of alleged oncogenes and proto-oncogenes like the transcription factor Myc and families of enzymes operating during the cell cycle, such as mTOR kinases and others have been shown to participate in these interactions (Bradshaw & Prentis 1987, Hunter 1998, Malumbres & Barbacid 2001, Gabay, Li *et al.* 2014, Sever & Brugge 2015, Lavoie, Gagnon *et al.* 2020, Liu & Sabatini 2020). Altogether, the answers to the *how* question have provided a rich catalogue of participants interacting during the diverse phases of the cell cycle, a biochemical catalogue that keeps expanding and will continue in the foreseeable future.

6.2. Why do Cells Proliferate?

Returning to the question related to the control of cell proliferation formulated along the lines of *"why* does a cell proliferate?" it is necessary to *a priori* adopt a premise that would address the issue of the default state of cells, that is, *what do cells do when unconstrained?* Evidently, when researchers adopt a given premise, it represents a major theoretical commitment because such a choice determines what is to be explained and thus it necessarily guides research in a particular direction. For example, if one were to adopt proliferative *quiescence* as a valid premise, what needs to be explained in this context is what makes cells not be quiescent, that is, what makes them proliferate. As mentioned above, when microbiologists axiomatically acknowledge that the default state of unicellular organisms is proliferation, they do not need to search for stimulators. Counterintuitively however, for over a century, experimentalists working with cells from multicellular organisms have adopted *quiescence* as the default state of those cells. Therefore, they focused on identifying and characterizing alleged stimulators of cell proliferation.

What has been the traditional narrative in textbooks and research articles in this field regarding the *how* and *why* questions? These two highly relevant discrete questions have been either ignored altogether or were amalgamated into a single one, namely, *how* does a cell proliferate? (Malumbres & Barbacid 2001, Alberts, Johnson *et al.* 2008, Cross, Buchler *et al.* 2011, Hunt, Nasmyth *et al.* 2011, Weinberg 2014, Sever & Brugge 2015, Novák, Heldt *et al.* 2018, Liu, Michowski *et al.* 2019, Liu & Sabatini 2020)

6.3. Does the Empirical Evidence Support the Principle that the Default State of All Cells is Proliferation?

Estradiol-17beta target cell lines have been a reliable experimental model for assessing our claim that proliferation is the default state of cells. In serumless

medium, estrogen-target cells proliferate exponentially in the absence of estrogens. Meanwhile, the addition of estrogen-less serum inhibits their proliferation in a serum concentration dependent fashion (Soto & Sonnenschein 1985); physiological concentrations of estrogens cancel this inhibition. Another relevant example of proliferative control is represented by the role of erythropoietin in the regulation of the number of erythrocytes in the bloodstream; here, erythropoietin acts by inhibiting cell death and thus allowing for the constitutive proliferation of erythroid precursors to be expressed (Koury & Bondurant 1988, Williams, Smith *et al.* 1990). Additional experimental examples buttressing *proliferation* as the default state are the inhibition of fibroblast proliferation by homologous serum (Sonnenschein & Soto 1981), the "ground-state" of embryonic stem cells (Ying, Wray *et al.* 2008), the active induction of proliferative *quiescence* in lymphocytes (Yusuf & Fruman 2003), and the constitutive proliferation of epithelial cells of Hydra during starvation (Bosch & David 1984).

An additional helpful hint to decide whether the default state is either *proliferation* or *quiescence* is provided by the adoption of an evolutionary perspective on the subject. For centuries, naturalists and biologists have widely recognized a common property of living objects that distinguishes them from the inert; this property was their ability to generate actions, exemplified by their ability to proliferate and move, and to create their own rules, particularly the aim of maintaining themselves alive. This property is called normative agency (Soto & Sonnenschein 2018). As mentioned above, regardless of how the first cell (or protocell) was generated, it stands to reason to assume that about 3.8 billion years ago, in the midst of a prebiotic soup, such a cell must have had the constitutive property to proliferate and move. From an evolutionary perspective, the generation of multicellular organisms from unicellular eukaryotes involved the conservation of previously existing levels of organization (Nurse 1990, Sonnenschein & Soto 1999). The constitutive capacity of cells to proliferate within a multicellular organism must have remained unaltered and hence, their default state conserved. As mentioned above, this idea is supported by the high homology between the cell cycle effectors of yeast and human cells (Nurse 1990, O'Farrell 2011).

Additional arguments buttress the need for an overdue reassessment of the default state of cells in multicellular organisms. For instance, in multiple species embryos develop outside of the parental organisms, demonstrating that exponential proliferation in early development may take place in sea water (urchins) in the absence of alleged growth factors (Nesbit, Fleming *et al.* 2019). Later during development, as different tissues are formed, proliferation is distinctively regulated suggesting that, with the emergence of multicellularity, inhibitory controls impose an induced quiescent state upon different cells in specific tissues. Once these cells become "freed" from organismal restraints, they manifest their default state by proliferating, as they do when explanted into routine culture conditions.

Conclusions

For over a century, research on cellular biology has been conducted under the premise that *quiescence* is the default state of cells in multicellular organisms (plants and animals). In contrast, microbiologists axiomatically acknowledge that the default state of unicellular organisms is *proliferation*. Moreover, no cogent argument has been offered so far that would justify a radical switch of the ancestral default state of cells with the advent of multicellularity. Notwithstanding these theoretical and empirical arguments, proliferative *quiescence* remains at the core of teaching at all levels of education and of research projects in developmental biology and as a basic premise of the currently hegemonic theory of carcinogenesis, i.e., the somatic mutation theory. Our analysis of this situation suggests that the adoption of this wrong premise might be responsible for the conceptual confusion in the fields of a) developmental biology, especially about how size and shape of tissues and organs are regulated and b) carcinogenesis. It follows that a radical theoretical change in biological thought is necessary regarding how the control of cell proliferation is regulated; this reassessment should contribute to resolving this crisis. As presented above, evolutionarily relevant alternatives are available and supported empirically. They rely on adopting *proliferation* as the default state of *all* cells.

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Perspectives and Hypotheses

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What is the Value of Science?

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Abstract

In our time, scientific research is positively valued as long as, and to the extent that, it has fruitful implications for the development of technology. This is what we may call "the technological assessment of science", or "technologism", for short. I contend that this assessment, so widespread today, stems from a serious error of appreciation, both historically and epistemologically, in ignoring the genuine nature of science—a mistake that can lead, and indeed has been leading for a few decades, to the impoverishment of the scientific spirit and of culture in general.

Keywords: science, technologism, culture

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> Wir müssen wissen, wir werden wissen
> ("We must know, we will know")
> Epitaph on David Hilbert's tomb

Introduction

In our time, the view that the scientific spirit is an important component of human culture that deserves to be valued positively is widely held (at least in those regions of the world that are not yet subjugated by Islamic fanaticism, nor by evangelical fundamentalism). At the same time, however, this positive assessment of science is often subsidiary with respect to the equally positive assessment of technology; that is, scientific research is positively valued as long as, and to the extent that, it has fruitful implications for the development of technology. This is what we may call "the technological assessment of science", or "technologism", for short. I contend that this assessment, so widespread today, stems from a serious error of appreciation, both historically and epistemologically, in ignoring the genuine nature of science—a mistake that can lead, and indeed has been leading for a few decades, to the impoverishment of the scientific spirit and of culture in general.

1. Terminological and Conceptual Precision

Before moving on to developing the argument, it is appropriate to establish some terminological and conceptual precisions to clarify the picture. To begin with, by "science" I mean the totality of scientific disciplines represented in universities and other advanced research institutions. Within academic science today, we may identify the following groups of scientific disciplines: "formal sciences" (logic and mathematics), "natural sciences" (physical-chemical sciences, Earth sciences, life sciences, individual psychology), "social

sciences" (social psychology, economics, sociology, ethnology, linguistics, philology, historical sciences), and "interdisciplinary sciences" (especially computer science, certain parts of philosophy, such as the philosophy of science and the philosophy of language, and the cognitive sciences). From a historical point of view, some of these sciences were already consolidated in Hellenistic times (from the 4th century BC on), especially with regard to mathematics, astronomy and some elementary portions of physics and physiology. However, the great boom in the scientific spirit did not occur until the 17th century, first in Western Europe, and later on it developed and expanded across almost the entire planet until the mid-20th century, when a period of lethargy began, to which I will return below.

The other term that requires clarification from the outset is "technology". Nowadays, in current English, the terms "technics" and "technology" are often equated, or else the second is used exclusively to the detriment of the first, but they should be clearly distinguished. "Technics" comes from the Greek "*tekhné*", the art (learned and transmitted from generation to generation) of knowing how to make things or of knowing how to manipulate them. For the Greeks, *tekhné* had nothing to do, neither positively nor negatively, with *epistéme*, which approximately corresponds to our term "science". In this sense, there has been technics since Homo Sapiens appeared on Earth; in fact, the much older Homo Habilis (which for some reason is called so) is likely to have used technics too. However, only since the Neolithic there was an explosion of technical innovations extremely important to Humanity: from the wheel to the printing press, through irrigation systems, the construction of large buildings, sailboats, hourglasses, hoes, gunpowder, and so many others. None of those novelties had anything to do with science. Not even the steam engine, the most revolutionary of the inventions of modernity, qualifies as an example of the benefits of science to technics, as is sometimes assumed: indeed, the branch of science that adequately accounts for the functioning of the steam engine is thermodynamics. However, James Watt invented the definitive model of that machine around 1775, that is, three-quarters of a century before the consolidation of thermodynamics as a scientific discipline (mainly thanks to the theoretical work of Hermann von Helmholtz, Lord Kelvin and Rudolf Clausius in the middle of the 19th century). In sum, the great technical developments that took place over several millennia before the first attempts at a genuine form of science in the Hellenistic era, and even a couple of millennia *after* that time, had nothing to do with the scientific spirit. It is true that the example of Archimedes, in the 3rd century BC, is sometimes mentioned as that of someone who was both a scientific genius (the greatest of antiquity, indeed) and an astonishing inventor of machines; but this actually is a unique example in antiquity, and it is also known that Archimedes himself belittled his technical achievements and wanted to be remembered exclusively for his contributions to *epistéme*—specifically to mathematics and physics (Störig 1957, p. 112).

2. The Scientific Revolution and the Advent of Technology

We therefore find that technics, in a genuine sense, has nothing to do, neither historically, nor conceptually, with the scientific spirit. On the other hand, the cultural form which certainly has a lot to do with science, is *technology*. It is therefore appropriate to distinguish clearly between technics and technology: technology is applied science; or, if one prefers, it is a very special form of technics that presupposes some scientific knowledge.

When and how did technology historically emerge? It is often assumed that this took place in Western Europe with the rebirth of the genuinely scientific spirit. This rebirth occurred after the deep lethargy of more than a thousand years caused by the combined blows of the Christian dogmatism that followed the collapse of the Greco-Roman civilization and the barbarism of the Germanic tribes, blows from which Europe only very gradually revived. This renaissance, which took place in the 17th century (and which is not to be confused with the artistic and literary Renaissance that had flourished more than a century earlier), is often referred to as "the Scientific Revolution". This latter revolution is supposed to have generated great technological advances, in the sense of technology that we have just defined. It is often mentioned that Francis Bacon's publication of his *Novum Organum* in 1620 and the famous motto attributed to him, "*scientia est potentia*", promoted the alliance of the new scientific and the technological spirits. Now, it is worth noticing that Bacon was not a scientist, let alone a technician. He was a politician and a literate, who, by the way, had a great aversion to the sciences of ancient Greece,

which he considered useless for the promotion of human well-being. Being vehemently opposed to the spirit of ancient science, he wanted to impersonate the herald of a new era. On the one hand, Bacon certainly had the merit of popularizing the importance of the experimental method in science (although he himself did not conduct any noteworthy experiment); but, on the other hand, he did not understand at all the decisive role of mathematics in the empirical sciences, nor did he realize the revolutionary significance of the discoveries of his genuinely scientific contemporaries, such as Kepler and Galileo. More than the promoter of the new scientific spirit, Bacon was the remote forerunner of what I have called "technologism", as evidenced beyond doubt by his apodictic affirmation: "the true and legitimate goal of science is nothing more than to give human life new inventions and resources" (Störig 1957, p. 223—my translation).

If Bacon was therefore not the champion of the Scientific Revolution, and not even a valuable assistant, who were its protagonists? Well, they were essentially those men whom Arthur Koestler once called "the sleepwalkers" (Koestler 1959), because, without realizing it, they walked firmly down the right path to reach the right goal. The "sleepwalkers" of the seventeenth century, which Koestler explicitly deals with in his book, are: Johannes Kepler, Galileo Galilei, René Descartes and Isaac Newton. To them we could add other champions of the new scientific spirit in the 17th century, not as popular as those mentioned, but very decisive too, namely: William Harvey (for human physiology), Robert Boyle (for chemistry) and Christiaan Huygens (for optics and mechanics). Besides being a scientist, was any of them a technologist? Only one of them, Huygens, may be described *cum grano salis* as such, because he invented the pendulum clock; however, what he was most interested in was not the measurement of time, but the development of the wave theory of light, as well as the solution of certain mechanical problems (like the right formulation of the laws of collisions and the analysis of centrifugal forces), all of which did not induce him to invent any machine. Of all the other "sleepwalkers" of the Scientific Revolution of the 17th century, there is not one whose name may be associated with a technical invention. Not even Galileo, to whom some texts of scientific popularization still today attribute the invention of the telescope: Galileo did not invent the telescope; what he did was to use the telescope that someone else (it is not known for sure who, probably a Flemish craftsman) had invented a few years earlier. In addition, Galileo used this invention not to improve the human condition, as Bacon would have wanted, but to focus it on the Moon and the stars, and thus discover that the surface of the Moon is comparable to that of the Earth (with its mountains and valleys) and that there were a number of stars far superior to what had previously been assumed. That is, Galileo made an essential contribution to the increase of human knowledge, not to the improvement of human well-being.

So, if it was not in the century of the Scientific Revolution that science and technics mated, was it then in the next century, the 18th century? The answer is equally negative. We have already seen that the greatest invention of the 18th century, the steam engine, had nothing to do with any scientific theory, either contemporary or of earlier date. And of the great scientists of the 18th century, namely the Bernoulli, Euler, Lavoisier, Coulomb, Buffon, etc., none of them can be said to have made a significant contribution to the technics of their time. Only Benjamin Franklin (who, by the way, was not a great scientist) contributed to technology by inventing the lightning rod, but apart from the fact that it was a rather casual invention, Franklin's own electricity theory, the so-called "theory of the two fluids," soon turned out to be entirely mistaken.

The same goes, *mutatis mutandis*, for the first half of the 19th century. Let us ask: what does the railway owe to contemporary or earlier scientific theories? Nothing. And the steamship? Nothing. And the cure of smallpox? Nothing. And, for the great scientists of that time—the Cauchy, Laplace, Dalton, Fourier, Clausius, Helmholtz, Darwin, ...—what machine did they invent or what disease did they cure? None. Only the great mathematician Karl-Friedrich Gauss can be said to have made a timid technical contribution, based on his knowledge of electricity theory: a primitive form of a telegraph, which in practice, however, proved to be useless; actually, we owe the telegraph as we know it today to Samuel Morse, who was not a scientist, but a sculptor.

It is only during the second half of the 19th century that the first attempts at a systematic use of scientific theories for technical developments began. Some entrepreneurs and politicians, who saw in scientific

discoveries (at least in certain areas of physics, chemistry and physiology) a possible (indirect) source of benefits, began to take a genuine interest in science. And this is how the alliance of scientists, engineers, doctors, entrepreneurs and even some clairvoyant politicians began to consolidate—and the result of that heterogeneous confluence is what we can genuinely call "technology".

Perhaps the first, or at least the most notorious and influential example of this new spirit of alliance between scientists, engineers and politicians was the deployment of the underwater telegraph between Britain and the United States in 1866 thanks to the scientific advice of William Thompson (later honored with the title of "Lord Kelvin"), who was already renowned for his contributions to a discipline very different from (and independent of) communication technology, namely the foundations of thermodynamics. Thanks to Kelvin's great influence, the decision of the University of Cambridge to establish, in the course of the 1870s, the Cavendish Laboratory, with the explicit purpose of constituting a coalition of scientists, engineers, entrepreneurs and officials for the promotion of applied science as an economic value took place (for more details, see Ball 2019, p. 29). This happened not before the last third of the 19th century. A contemporaneous parallel development took place in Germany, mainly due to the great influence of the pathologist Rudolf Virchow, though not in the area of physics, but in the coalition of the life sciences and medicine.

This is how in the second half of the 19th century, the first successful bases for the cooperation between scientists and technicians (in a broad sense of the term "technician", encompassing all kinds of engineers and medical doctors) began to be settled. It was on these bases that the 20th century turned out to be the first great century of technology. It would be ridiculous to list all the inventions made throughout the 20th century that were inspired by the many scientific theories proposed during that period or before. It suffices to mention only a few of the technological developments which have profoundly transformed the daily lives of humans: from radio to computers, through television, antibiotics and nuclear power plants. None of these inventions could have been conceived and implemented without the background of one or more previous solid scientific theories. This is what technology means, and this is what is characteristic of the 20th century and, perhaps, stretching this fecund period into the past, of the second half of the 19th century, *but of no previous era*.

3. Science as Fundamentally Independent of Technology

Now, when focusing on the development of science from the mid-19th century to the present day, we can see a few branches of science that came to extraordinary results, but have little or nothing to do with contemporary or subsequent technical inventions. A notorious case is, of course, that of the formal sciences—logic and mathematics—which since the mid-19th century had a boom incomparably superior to any previous development since the Greeks, but completely oblivious to any technological application. For example, one of the deepest contributions to logic and mathematics in the 20th century were the theorems of the completeness of first order logic and of the incompleteness of arithmetic that Kurt Gödel proved in 1930/31. Now, ninety years later, these famous theorems so far show to be completely irrelevant to any technological application. It is true that shortly after Gödel's proofs, there were some developments in the new logic and the foundations of mathematics that used similar formal techniques and that, in the long run, would lead to technological applications in the area of Artificial Intelligence; the most notorious case is, of course, that of the Turing machines; but Gödel's completeness and incompleteness results as such were irrelevant to these later developments.

The same goes for another discipline located at the opposite end of the range of sciences, far removed from mathematics but equally independent of applied science, namely, philology. Indeed, for the proof that all those languages known as "Indo-European" or "Indo-Germanic" have a common origin in a primal language, the "proto-Indo-European" (a language already lost nowadays, but that undoubtedly existed), the philologists of the second half of the 19th century and early 20th century (especially Franz Bopp and August Schleicher), who obtained this result after long and admirable efforts, did not promote any technical application of their discovery, and it is difficult to imagine to what new technology the identification of the proto-Indo-European could lead.

In the case of those scientific disciplines of which it is traditionally claimed, or simply assumed, that they are closely linked to technology, as is often assumed of the natural sciences, we will encounter so many exceptions that we could not even say that they confirm the rule. One of the best confirmed theories of biology that has deeply marked mankind's self-image is undoubtedly Charles Darwin's theory of evolution. Now, what is the machine or instrument that has been built thanks to this theory? The question is obviously ridiculous for being totally out of place. Only in the field of preventive medicine when dealing with pathogenic microorganisms it may appear that the principle of natural selection could be relevant for certain therapies, but these are rather marginal studies. In any case, to the vast majority of practicing physicians (i. e. technicians devoted to the healing of the sick), the theory of evolution remains completely irrelevant.

Even in physics, a discipline which many people think of when talking about the benefits that science brings to technology, we face more than one good example of irrelevance or very little relevance of science to technological developments. The two most fundamental and best-confirmed physical theories in human history are Albert Einstein's general theory of relativity, on the one hand, and the theory often referred to as "the standard model of particle physics" (in the following abbreviated as "SMPP"), on the other hand, developed in the 1960s primarily by Murray Gell-Mann, Sheldon Glashow, Steven Weinberg and Abdus Salam. Now, with regard to generalized relativity, it should be noted that Einstein formulated his theory in 1915, and very soon (in 1919) it would be brilliantly confirmed and celebrated by the scientific community as a huge scientific advance. However, only 80 years later it would be found that such a theory may have some technological relevance, albeit a very secondary one indeed, by helping to design the GPS satellite location systems. (In fact, GPS systems also may be developed without taking into account the fundamental equation of generalized relativity.) And as far as the SMPP is concerned, 60 years after its conception, we still are waiting for someone to tell us what its technological implications are. There certainly are some notable technological applications of (classical) quantum mechanics, like the laser, but this is a technology which was developed before the advent of the SMPP; also, there is certainly much talk nowadays about the prospects of developing so-called "quantum computers", but leaving aside the fact that they still are rather a promise than a technological fact, they would be an application of classical quantum mechanics and not of the SMPP as such.

In other cases, we can certainly point to very important technological developments based on pure science research, but in such a way that these researches were conducted with complete independence from any objective of technical application long before its technological possibilities were revealed. This is the case of the discovery and study of radioactivity in the late 19th and early 20th centuries by Henri Becquerel, and the couple Marie and Pierre Curie: only several decades after their scientific discoveries it turned out that radioactivity could be technologically relevant (whether for the construction of nuclear weapons or for cancer treatment) after Otto Hahn and Fritz Strassmann discovered the possibility of the nuclear fission of uranium in the late 1930s. It is noteworthy that neither Becquerel nor the Curies would have ever thought of such applications.

In other cases, technical inventions have had some relation to previous scientific inputs but they are so only in a much more indirect way than is usually assumed, and also often not with the theory considered to be the most valid and important in the domain in question. For example, it is true that Thomas A. Edison could not have thought in the late 19th century of making an incandescent electric lamp if he would not have taken into account Ohm's law established at the beginning of the same century. However, the really fundamental theory in this field, namely J. Clerk Maxwell's electrodynamics, published a few years before Edison's invention, served this inventor no good. In other cases, the scientific theory that inspired a technical invention later turns out to be completely false; this was the case already alluded to above of Franklin in the 18th century, who invented the lightning rod inspired by the theory of the two electrical fluids—a theory that would be abandoned soon afterwards...

Let us now summarize what the examples set out above, as well as many others that could be brought forward, show about the supposed linkage of scientific progress with technological progress. In many recognized scientific disciplines there is virtually no link between the two areas; others contain examples of a strong linkage, but also other examples (within the same discipline) of lack of linkage, or of not quite

significant linkage, or even of an erroneous linkage between a technical invention and a false theory. It then follows that the essential function of science, at least as the cultural form that Humanity has known since the Hellenistic period, or since the 17th century at the latest, is not to be the advance of knowledge applied to technical developments. Science sometimes lends itself very well to being applied technologically, other times it lends itself only a little, and in still other cases it does not lend itself to it at all. But in any case, applicable or not, applicable to a greater or lesser extent, applicable in the short or in the long term, that which is the main mission of science, and therefore its true value, is not to contribute to technological developments. This is, at best, a side effect of science (welcome to some, disliked by others), but which in any case should not affect our assessment of the scientific theories that are at the basis of such developments. Maxwell's electrodynamics is no more valuable than the general theory of relativity because the former has driven the invention of things like radio and television, and the second has not.

4. The Genuine Value of Science

So, if it is not technology that can give meaning and value to scientific knowledge, where does the essential value of science come from—if it has any at all? In the Platonic-Aristotelian tradition, *epistéme*, the historical ancestor of our *scientia*, was characterized as the reasoned and well-justified knowledge of the essence of being. Certainly, today we would use a less metaphysical language, albeit still inspired by the Greek tradition, and we would simply say that *epistéme* or *scientia* is what provides us with a reasoned and well-justified knowledge of what really exists. But leaving aside historical-philological nuances, the purpose of our science is essentially the same as that of the Greeks' *epistéme*; only methods have changed. And even they have not changed drastically: at least since Hellenistic times, the Greeks already knew that mathematics and systematic observation are good tools for achieving solid knowledge. All they still lacked was the idea of controlled experimentation—with some notable exceptions, like the one exemplified by Archimedes. But even experimentation is not absolutely essential for attaining an adequate understanding of the scientific spirit; today, there are still a large number of disciplines considered as genuinely scientific, in which experimentation plays no role at all—from mathematics to linguistics through ethology and ethnology. In fact, our concept of science as the best way to achieve solid knowledge about what the world is like is not so different from Aristotle's. Deep down it is the same. Or at least it has been so until recently, because I must admit that my characterization of what is essential in the scientific spirit comes from a conception less and less shared by those responsible for the scientific policy of supposedly advanced States, by journalists, by those who write reports for ministries, in short, by most people who have some opinion on what science is, or must be. For all these people, science is, instead, nothing more than applied or applicable science. Their paradigm of what should be a scientific achievement is the hackneyed *Big Science* (which is basically nothing but large-scale technology), not the scientific theories as we knew them until the mid-20th century. I will next expand on this subject while documenting what we might consider a dangerous and costly misjudgment.

5. The Menace of Technologism

Technologism is an anti-Aristotelic alternative, a view of science, that, as alluded to above, was originally promoted by Francis Bacon at the beginning of the 17th century. Again, Bacon was not a scientist and, moreover, he was not fully aware of the true meaning of the Scientific Revolution that was taking place at that very time. He was, however, an equivalent of a modern, savvy PR man who greatly influenced the members of the contemporaneous *intelligentsia* and those who followed it. He inspired the phrase "science is power" which in fact meant that science could control Nature, a project that could be extended to human society. However, it is worth noticing that none of the true stars of the Scientific Revolution shared Bacon's view about the purpose of the sciences. For instance, Kepler did not propose to use the laws of the planetary orbits he had discovered to facilitate interplanetary traffic; Galileo did not focus his telescope on the Moon to heal the plight of lunatics; Descartes did not translate geometry into algebra in order to make the job of land-surveyors easier; Huygens did not investigate optical phenomena in order to provide corrective lenses to myopes; and Newton did not apply the law of gravitation he had discovered to tides in order to prevent shipwrecks. Notwithstanding these factual

precedents, the Baconian doctrine was successfully adopted even by talented scientists who addressed heads of states, ministers, businesspersons, reporters, philanthropists, and anyone who could be sensitive to the "science is power" fake.

We may see the roots of this misrepresentation of the truly scientific spirit (a misinterpretation endorsed by many scientists themselves) in the fact that science is not practiced in a social vacuum, far from it. Indeed, the practice of theoretical and empirical research is costly. Scientists and their bureaucratic representatives are in need of funds to pay salaries to themselves and their collaborators, to the institutions that host them (the so-called indirect costs), and to purchase consumables and equipment. Consequently, sadly enough, it would seem as if scientists have subconsciously internalized Bacon's views to the point at which the unencumbered scientific goal becomes secondary to the need to maintain afloat the scientific enterprise that allows genuine original science to thrive. Unless corrective action is adopted soon, creative science will likely be reduced to applied science, that is, technology. Under these stressful circumstances, fundamental knowledge, that is the non-utilitarian goal of scientific research, will tend to disappear from our culture. More troublesome, the notion of "science for the sake of science" may become incomprehensible to future generations.

6. The Stagnation of the Genuine Scientific Spirit

Based on an analysis of developments that have taken place during the last one hundred years, we may reach the sad conclusion that the threat represented by technologism replacing science has been intensified in the last decades. Certainly, our perception of a "progressive stagnation of the scientific process" may be regarded by some inside and outside the academic community as just an exaggeration. After all, widespread comments by the specialized press, newspapers and magazines insist in highlighting alleged breakthroughs that have taken place along the length of the 20th and the current centuries. However, if one focuses on momentous discoveries that have taken place during the 20th century and to what has happened as far as scientific breakthroughs during the current century, the picture is rather murky. In fact, unequivocal signs of scientific stagnation are becoming increasingly obvious. To be more precise, the stagnation process in the sciences has become more notorious after the first two thirds of the 20th century have elapsed. Certainly, if we would agree that the 17th century could be considered as a *saeculum mirabilis* for science, a comparable evaluation should be extended to the first two thirds of the 20th century. We may arbitrarily point to 1966 as a conventional temporal limit for exceptional scientific contributions or startling discoveries followed by a mediocre period. And now, let us document this claim.

Let us start by examining what has happened in the formal sciences, namely, logic and mathematics. Truly revolutionary contributions in these sciences have taken place without exception in the first 2/3 of the 20th century. In 1901, Bertrand Russell discovered the paradox that carries his name that shook the foundations of logic and mathematics; next, between 1910 and 1913, again Russell and Alfred N. Whitehead published the *Principia Mathematica*, a monumental exposition of the new logic and its application to the foundations of mathematics. Then, from the beginning of the 20th century to the 1930s, Ernst Zermelo, John von Neumann and a few others axiomatized set theory as we know it today. In the 1920s, David Hilbert and his disciples developed proof theory, exceedingly important for the foundations of mathematics. In the early 1930s, Gödel proved his famous theorems, probably the deepest contribution to the understanding of the nature of logic and mathematics. In 1940, again Gödel showed the consistency of the so-called "continuum hypothesis" with the other axioms of set theory. Between the 1940s and 1950s, the self-described "N. Bourbaki" group reconstructed all of mathematics in a unified fashion based on set theory. In the 1950s, the theory of categories was developed as a general alternative to set theory. In 1963, Paul Cohen proved that the continuum hypothesis is independent of the other axioms of set theory, a truly intriguing result. In the 1950s and 1960s, Alexander Grothendieck, who many consider the greatest mathematician of the 20th century, published his most revolutionary works on algebraic geometry and topology, which earned him the Fields Medal just in 1966, our "hinged year"; it is symptomatic that, after this date, Grothendieck's contributions became less numerous and less significant, and that he soon after voluntarily withdrew from active research... And now, let us ask ourselves, what fundamental contributions have been made in mathematics since the 1970s? Undoubtedly,

some interesting specific results have been obtained such as the proof of Fermat's theorem, or some further developments in category theory; however, none of this is comparable to the accomplishments that took place during the two first thirds of the century.

Let us now move on to the contributions in the physical-chemical sciences. In this field, the contrast between what can be considered as significant contributions in the third part of the 20th century plus the two decades of the 21st century and the first two thirds of the 20th century has been even more spectacular. Absolutely all the fundamental theories about space, time and matter that have revolutionized our understanding of the Universe were proposed *and confirmed* during the first two thirds of the century. In 1905, Albert Einstein enunciated the special theory of relativity; next, in 1915, Einstein again proposed the general theory of relativity that was verified in 1919 by Arthur Eddington and his group through careful astronomic observations. In astrophysics, based on Einstein's general theory of relativity, Georges Lemaître formulated in the 1920s the Big Bang hypothesis that was empirically confirmed by Edwin Hubble in 1929.

Moving on to a completely different branch of physics, namely, quantum physics, it can be noticed that the first version of quantum mechanics was due to the contribution of Max Planck in 1900; the definitive versions of this theory, namely, the matrices mechanics of Werner Heisenberg and the undulatory mechanics of Erwin Schrödinger were independently and simultaneously built at the end of the 1920s. Then, in the 1930s, P.A.M. Dirac established the basis of quantum electrodynamics which allowed the unification of quantum mechanics and the special theory of relativity. Later, the Standard Model of Particle Physics (SMPP), a genuine fundamental theory (and not just "a model"), considered as the most successful theory ever in physics, was gradually constructed beginning in 1961 when Gell-Mann introduced the notion of weak interaction. Shortly thereafter, Glashow unified the electrodynamic phenomena with the weak interaction and Gell-Mann formulated the quark hypothesis. Finally, Steven Weinberg and Abdus Salam published in 1967 (only one year after our arbitrary selection of 1966 as the end of the great scientific contributions in the 20th century) the synthesis of the three great types of interactions, namely electromagnetism, the weak and the strong interactions (for more details about these last developments, see Moulines 2016, pp. 955-956). It is worth calling attention at this point that, after the unification of the three mentioned interactions within the frame of the SMPP, most physicists thought that one more step could be promptly made, namely, the unification of these three basic interactions with the oldest one known, i.e., gravitation, which is dealt with by another (ontologically and methodologically) quite different theory, namely, the general theory of relativity. The expectation by physicists during the last third of the 20th century to find a way to unify both theories either by showing that the general theory of relativity could be "reduced" to a slightly modified version of the SMPP or, alternatively, that a providential untapped genius or a group of geniuses would be able to formulate a novel Great Theory (the famous "theory of everything") that would encompass the SMPP and the general theory of relativity as special cases—a new great theory able to be empirically verified—did not materialize despite the concerted efforts invested in this direction. Indeed, unifying theories such as the various versions of the so-called "string theory" and the notion of the "multiverses", starting in the 1970s, as a matter of principle may not be tested empirically, a fate recognized even by their own originators. Thus, it would appear as if, during this period, at least a group of mathematical physicists would have become exalted metaphysicians using rigorous mathematics indeed, but remaining nevertheless hard-nosed metaphysicians with no connection with empirically testable facts. This alternative has nothing to do anymore with physics as an empirical science, at least as judged from what we have learned from Archimedes, and later on from the developments that took place during the 17th century.

Always within the physical-chemical sciences, but essentially independent of relativist and of quantum physics, there is a branch that deals with irreversible processes, namely what is usually called "non-reversible thermodynamics". It is essentially devoted to the study of chemical and biochemical processes. It originated in the 1930s with the so-called "reciprocity relations" of Lars Onsager which were later refined by Ilya Prigogine's significant contributions in the 1940s and 1950s. No new important theoretical breakthrough in non-equilibrium thermodynamics has occurred after those introduced by the pioneering contributions of Prigogine and his disciples.

In sum, no highly significant theoretical advance has been recorded in physics and chemistry in the last third of the 20th century and during the two decades of the current one. Admittedly, a few noteworthy discoveries did take place in this period such as the detection of the Higgs boson in 2012, which definitely confirmed the SMPP, and the first more or less direct observations of black holes between 2016 and 2019. It should be noted, however, that none of these late discoveries are comparable to the breath, depth and innovative significance of those mentioned above that took place in the first two thirds of the 20th century.

Regarding the earth sciences, their fundamental theoretical paradigm continues to be the continental sliding slabs theory formulated in 1912 by Alfred Wegener, which was acknowledged to be reliable shortly after the end of WW II. No significant new development in this field has been recorded after this momentous event took place.

Let us now move on to crucial developments that occurred during the last 120 years in the life sciences with the purpose of determining whether they offer the same diachronic pattern seen in mathematics and in physics. Without entering into details, suffice it to remember that a reliable formulation of Mendelian genetics and its empirical confirmation took place during the first two decades of the 20th century with the theoretical work of, among others, William Bateson and Hugo De Vries, and empirically by Thomas H. Morgan and his collaborators around WW I. Later on, in the 1930s and 1940s, a combination of genetics and evolutionary biology opened the way for population genetics thanks to the far-reaching theoretical and empirical contributions due to Theodor Dobzhansky, J.B.S. Haldane, Robert Fisher, Ernst Mayr and George Simpson, who generated the so-called evolutionary modern synthesis. Also, in the 1930s, ethology was created thanks to the leadership of Konrad Lorenz in Vienna. And finally, after the crucial identification of DNA as the carrier of the genetic material by Oswald Avery's group in 1944, it was in the 1950s that Rosalind Franklin, Francis Crick and James Watson developed the bases for the so-called Molecular Biology Revolution by describing the correct double helix structure of the DNA molecule. Decades later, this branch of biology culminated in a technological bonanza that is currently applied to the fields of medicine (diagnostics, vaccines, etc.), agriculture (nutrition, etc.) and other domains. Next, it can be considered that Conrad Waddington's introduction of epigenesis in the field of development in the 1950s and 1960s qualifies as a significant seminal contribution. Realistically, however, has it been any conceptual contribution in the life sciences since the 1960s that could be recognized as earth-shattering like the previous ones?

In the field of psychology, psychoanalysis already flourished before WW I and the behaviorist paradigm emerged shortly thereafter. Now, regarding the subject of cognitive psychology, it is generally acknowledged that it has its roots in the pioneering contribution by Warren McCulloch and Walter Pitt who in 1943 introduced the neuronal network theory which was later on enriched by the initial developments of artificial intelligence by John von Neumann, Norbert Wiener and others toward the end of the 1940s. These days, claims about a grandiose new cognitive paradigm tend to ignore that the basic elements of cognitive science were already in place well before 1966, our arbitrarily designated limit for truly revolutionary contributions in the sciences at large. It would probably be more realistic to consider that ever since the pioneering contributions generated before 1966 in cognitive science, a process of confirmation and data refinement took place thanks to the incorporation of the novel technological marvels of brain imagery. In his recently published book *The Idea of the Brain*, the neurobiologist and science historian Matthew Cobb summarizes the situation in the cognitive sciences by concluding: "No major conceptual innovation has been made in our overall understanding of how the brain works for over half a century" (quoted by Philip Ball in Ball 2019, p. 31). This harsh judgement may certainly appear to be a bit too exaggerated, but it seems to me that it responds to a widespread feeling among the specialists in this area.

Let us consider now the social sciences. In order to reflect about presumably significant developments in these disciplines, it might be useful to recall the ideas advanced by Thomas S. Kuhn in his influential book *The Structure of Scientific Revolutions*, whose first edition was published in 1962, that is, just before our 1966 limit settled above. According to Kuhn's views at that time, the social sciences were in a "pre-paradigmatic" stage because the respective scientific communities were not yet unified in acknowledging which were the fundamental concepts and principles in each one of the relevant fields, which were the basic questions to

be answered and which were the methods that could tentatively shed light on those questions. It is worth recalling that in the 1960s, Kuhn's views cautiously implied that at least some of the branches of the social sciences would soon reach a true paradigmatic stage by agreeing on the three elements just mentioned. Realistically, however, it might be fair to recognize that 60 years after such optimistic prediction no such change has been generally acknowledged in the social sciences. Admittedly, at some point, Noam Chomsky's model of generative-transformational grammars in linguistics seemed to reach the desired paradigmatic stage. However, as of today, Kuhn's prediction has not materialized even for linguistics if one realizes that a multitude of well-regarded linguists from all over the world do not relish listening to generative-transformational grammars.

Equally questionable are unsubstantiated claims that, during the last decades, the so-called economic sciences have reached a paradigmatic stage. One may seriously consider this claim if one narrows it down to the developments in microeconomy, and more specifically, in the combination of decision theory with game theory. (Incidentally, these theories were proposed already in the 1950s.) However, if we keep in mind developments in macroeconomy (which is what people normally think about when referring to theories of economics), it should be acknowledged that for decades now there has been an implacable competition among at least three alleged paradigms or general views, namely, the classical neo-liberal of Friedrich Hayek and others, the Keynesian, and the (crypto)Marxist of Thomas Piketty, for example. Clearly, they all originated in approaches dated from before 1966. Altogether, it could be safely concluded that no successful paradigm in any of the social sciences has materialized since their premature anticipation by Thomas Kuhn in the 1960s.

7. John Horgan's View on the Stagnation of Science

Within the context of this essay, it is legitimate to ask whether the tendency toward a progressive stagnation of the genuine scientific spirit is a temporary, fleeting phenomenon, or does it have profound historical and social roots? Despite clear evidence for the patent science stagnation phenomenon, it is puzzling to notice how rare has been a rigorous analysis of it by scholars in the field. Perhaps, the exception in this regard has been the systematic analysis of the subject by the scientific commentator and historian of science John Horgan who in 1996 published a book provocatively entitled *The End of Science: Facing the Limits of Knowledge in the Twilight of the Scientific Age*. Essentially, he explained the stagnation of the sciences as a result of the combination of two endogenous processes. One of them relates to the assumption that in certain areas, such as particle physics and molecular biology, the fundamental laws that have already been uncovered fulfill all the explanatory requirements of the subject. The argument follows that those disciplines have reached an optimum of consolidation and confirmation *ad vitam aeternam*, and that, therefore, what remains unknown are just little complimentary details, that could be translated pejoratively as "mop-up operations". In addition to this depressing interpretation, Horgan also entertains the notion that the scientific enterprise in general has reached a degree of sophistication that prevents the human intellect to surpass the natural limits of human cognition. In other words, until a few decades ago, difficult but not insoluble problems could have been resolved when a single genius, or a group of collaborating geniuses, could propose and verify a highly complex theory. However, according to Horgan, in the recent past, the complexity of the problems faced by scientists is such that explanations of those subjects are beyond the intellectual capacities of humans. Thus, in our times it would be unimaginable the arrival of a Darwin, a Hilbert, an Einstein, or a School of Copenhagen capable to resolve them successfully.

Historians of science, practicing scientists and the educated public already know about arguments like the one Horgan advanced regarding the limitations of the human intellect either to make further substantial progress, or else to resolve yet to be explained scientific issues that have become too complex for the human mind. As is widely known, a comparable view arose toward the last third of the 19th century triggered by physicists who prematurely considered that the fundamental laws of physics had already been proposed and verified, and that only unimportant details were still to be resolved. It is well-known that the German professor of physics Philipp von Jolly emphatically recommended his young pupil Max Planck not to

devote his career to physics, since, supposedly, no interesting new developments could be expected in this discipline (Planck 1950). And again, the argument that science had reached its intrinsic human limit became popular among European intellectuals and scientists, initially in German speaking countries and later even more acutely in France. More specifically, when the famous Swiss physiologist Emil Du Bois-Reymond examined basic questions regarding the essence of matter, life and conscience, he was quoted as stating the famous phrase "*Ignoramus et ignorabimus*" ("we ignore and we will ignore") (Du Bois-Reymond 1872). During those years, other intellectuals and scientists, especially in France, also stated that science in general was bankrupt (Otero 2011). Shockingly, however, only a few years later, at the beginning of the 20th century, very important theoretical developments in science took place such as the introduction of mathematical logic, the strengthening of set theory, as well as the creation and confirmation of the relativity theories and of quantum physics in the basic sciences. Meanwhile, the development of genetics revolutionized the field of biology. On the one hand, one wonders whether the pessimistic current views of John Horgan are a re-edition of the myopic views of Phillip von Jolly, Du Bois-Reymond and the French "bankruptists" of the 1890s. On the other hand, leaving Horgan's pessimistic views aside for the moment, we should give him deserved credit for having diagnosed early on the stagnation of the sciences in the last decades. We might differ however on identifying the etiology of the phenomenon. Neither the current stagnation nor the one diagnosed by Jolly, Du Bois-Reymond or the "bankruptists" of the end of the 19th century were due to an inherent (and unavoidable) evolution of the scientific spirit. Further, it seems unlikely that at the end of the 19th century or today, simultaneously, all the sciences may have ended up in an intellectual cul de sac. Due to what metahistorical and/or metascientific miraculous coincidence sciences that have nothing or little in common, from mathematics to ethology, going through physics, chemistry, geology, and biology, may have reached their explanatory limits at the same time? Moreover, each branch of these sciences has shown to develop following a very unique historical process. Indeed, mathematics as a scientific discipline dates back to the 6th century BC (that is, 25 centuries ago), scientific astronomy started developing in the 4th century BC (23 centuries ago), physics developed starting in the 3rd century BC (22 centuries ago), chemistry began developing in the 17th century (just 4 centuries ago), biology began as a science starting in the last third of the 18th century, that is two and a half centuries ago, and finally, scientific psychology developed in earnest toward the end of the 19th century (a little more than a century ago). It is, therefore, highly unlikely that these varied scientific disciplines might have imploded by having reached simultaneously the same intellectual obstructing wall.

8. Toward an Externalist Explanation for the Stagnation of the Sciences

Summarizing Horgan's thesis, an explanation for the current scientific stagnation suggests that it is due to factors inherent to the respective scientific disciplines. This represents an "internalist" explanation. However, the previous discussion of the historical and methodological data at hand suggests that Horgan's thesis is not plausible at all. It is preferable to consider, instead, first and foremost the external factors (social factors, that is) that might more realistically explain the stagnation that we both agree currently affects the sciences. By blaming external factors for the stagnation of the sciences, we may offer a tentative optimistic alternative in the sense that, once those factors identified, they may be susceptible of being corrected. In this regard, shortly before the beginning of WW II, J. B. S. Haldane, a widely praised physiologist and geneticist, anticipated that something undesirable was becoming evident about how public opinion was perceiving the role of the sciences in society. Here is an excerpt of his worrying premonitions:

> It is quite possible, I think, that as the ideals of pure science become more and more remote from those of the general public, science will tend to degenerate more and more into medical & engineering technology, just as art may degenerate into illustration and religion into ritual, when they lose the vital spark. (Haldane 1937, p. 119)

I share Haldane's diagnosis of the crisis that the sciences are now going through formulated more than eight decades ago, and I prefer it over the one Horgan advanced less than three decades ago. Moreover,

I propose to consider two important independent factors that, from an epistemic perspective, relate to the practice of the sciences and the social context in which the sciences are perceived; though they are methodologically independent, they mutually reinforce themselves. These two factors are, on the one hand, the above referred technologism that has overtaken the practice of the sciences, and on the other hand, what can be characterized as the competitive spirit under which the sciences are currently conducted.

The technologism factor has already been addressed above. Let us next deal with the second factor. In my view, this second factor is grounded on a mischaracterization of how the sciences should currently be appreciated and practiced. Namely, instead of classically considering science as a collaborative enterprise among scientists in search of truth, or at least an approximation to it, the current rationale to assure success in science considers that scientific progress will materialize only as a result of a ruthless competition among scientists. This competition could be exercised among separate individual scientists or between small groups with the aim of achieve prestige and/or financial support from governmental, philanthropic or big industrial funders. The necessary goals to obtain the prestige and the funds to initiate or to continue doing research do not in themselves have much to do with pursuing the search for truth or the objective knowledge of Nature. Instead, those goals are: 1) the number of papers published yearly in prestigious peer-reviewed periodicals (preferably in the Anglo-Saxon countries) by the scientist or the group of scientists considered, and 2) the number of times a publication by the scientist(s) in question is cited in the periodicals referred to above. The first criterion of scientific recognition has increased exponentially in the last decades while the second one, that we may baptize as *citalogics*, is increasing significantly as well. Actually, citalogics has become a recognized branch of the sub-discipline of sociology of science destined to assess the worth of scientists for governmental or business funding sources.

Citalogics, as a metascientific discipline, began in the 1970s/80s, but it became very influential after Internet and the Web of Science would turn to be the evaluators of records of scientists (at least in the so-called paradigmatic sciences). In 2005, Jorge Hirsch, a physicist, coined what became the *h index* aimed at quantitatively evaluate with objectivity the productivity of any scientist based on the number of her publications and the number of citations her publications accumulated over time. Ever since, the h index has increased its popularity and thus it has been used with increased frequency in university settings, and in industry and commerce. It has become obvious that under these circumstances, scientists in constant competition with their colleagues in the same area of research aim to increase their respective h index. This attitude prevents them from considering their colleagues as welcomed collaborators, as originally conceived by traditional science. Instead, fellow scientists in the same area of research become dangerous competitors. It then follows that in order to increase their respective h index researchers will tend to publish as many articles as possible on popular subjects susceptible to impress publication reviewers and those in funding "study sections". As a result of this mismanagement of values, it is not surprising that young researchers would avoid selecting difficult and/or esoteric research subjects where sure short-term success is problematic and chancy. Under these dangerous conditions, it is unlikely that young investigators would take the luxury of waiting two decades to publish their research efforts as Newton, Darwin and others did in the past to convince themselves of the solid quality of their results. As David Chavalarias and Philippe Huneman recently argued: "the perverse effect of the incitement to the race to publish leads almost mechanically to a decline of the quality of scientific production" (Chavalarias & Huneman 2020, p. 4—my translation).

On top of the pervasive influence of the two external factors referred to above that have decisively contributed to the current stagnation of the sciences, one may notice an additional serious detrimental outcome. Having to "sell" their research projects to their own competitors sitting in judgment in arbitrarily selected, conflicted "study sections", researchers are encouraged to oversell the merits of the areas of research they choose and promise improbable outcomes. The sad realities faced by researchers who apply for funds foster the adoption of a cynical attitude toward a situation in which applicants and funders (direct and indirect ones) accept the odious situation where each participant plays a role in a drama that is just a farce. This is hardly the way to do creative science.

Until a few decades ago, the dictum "Science for the sake of science", which derived from the previous one dated from Classical Antiquity positing "Knowledge for the sake of knowledge", was accepted by any minimally educated person. Despite repeated statements in the same sense, current public opinion appears increasingly dubious of such claims. Paradoxically, however, two other structurally analogous dictums, namely, "Art for the sake of art" and "Sport for the sake of sport", coined in the 19th and 20th century, respectively, enjoy a higher popularity than the much older one about science. As sketched in this essay, we may attribute this unfortunate development to technologism, on the one hand, and to the misguided competitive attitude prevailing in established research institutions, on the other. In a cynical twist, one may recognize a sort of late revenge by Francis Bacon. The situation that the principle "science for the sake of science" faces now is due to complex factors that prevent the fulfillment of the stated goals of scientists who decades ago explicitly understood and abided by the contract between scientists and the public who funded basic research. Current realities in the practice of science, in the political discourse, in the short-termism of the electorate, of the public opinion and of the media do not help much in restoring the tradition dating from the 17th century that would provide the basic seeds for "science for the sake of science" to restore its original intrinsic creativity.

Conclusions: is Here a Problem to be Fixed? If yes, by Whom?

The sciences have been one of the most important contributors to the development of humanity on planet Earth. Now, a number of arguments have been advanced in this essay that indicate that the sciences are facing short and long-term serious threats that question their viability in the midst of a decades-old period of crisis. These threats are generated by the same protagonists who have been and are still responsible for their perceived success, namely, humans. Simultaneously, humanity at large is also facing comparable threats to its viability in the form of climate change, pollution, and over-population. It is not an exaggeration to qualify these threats to human viability as real crises. The resolution of this wide-range threat will require the adoption of remedies that should address current shortcomings affecting all aspects of human activities. The sciences and the scientists should volunteer to play crucial roles in advancing theories, reliably collecting and interpreting data aimed to resolving intellectual unknowns on a long-term basis. The narrative just offered here implies that during the last half-a-century the virtues of academic scientific research have been replaced by the pursue of technological feats that do not address the sustainability of the heterogeneous components of humankind living in a biodiverse environment. A resumption of creative science may not by itself resolve the complex crisis humankind is facing. However, if the sciences could help in a communitarian effort in such direction, this will only take place in an atmosphere in which scientists are given the opportunity and the tools to generate knowledge without financial "strings attached".

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Epidemiology, Ecology, and Evolution of Human-Virus Interaction: An Overview of the Relevance to Human Health and Disease

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Abstract

Acquiring a systemic perspective on epidemic events is mandatory in an age in which such events are rapidly growing in both number and spatial distribution. In this work we describe the human/virus interaction through the 'deep time' of evolution. We show how ancient epidemics shaped animal and human biology influencing basic traits like multi-cellularity, immunity and cancer. Furthermore, on a much shorter time scale, we focus on the role played by globalization and anthropogenic environmental deterioration in the growing menace of recurring pandemics.

Keywords: retroviruses, cancer, biosphere, epidemics, prevention, SARS-CoV-2

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Introduction

Since the discovery of the tobacco mosaic virus in the last decade of the 19th century (Beijerinck 1898), viruses have been given an exclusively negative connotation for their tendency to cause dangerous diseases. Of course, no one can deny that viruses have caused and still cause suffering and death in human populations around the world. However, viruses do not exist to cause disease in humans and other organisms. They are biologically active molecular agents that lie on the border between the living and non-living world. Generally speaking, their major characteristics can be identified with *i)* their propensity for structural (genomic) change, *ii)* their ability to replicate and spread by infecting prokaryotic and eukaryotic host species, and *iii)* their need for a living host. Viruses elicit a remarkable interest in the biomedical field, However, a broader and more realistic view in recent decades emphasizes the essential role they play in ecological systems and biological evolution (Feschotte & Gilbert 2012). Epidemiologists gave a fundamental contribution to understanding viral diseases and their trends in human communities. However, the emergence and reappearance of many infectious diseases recorded in recent decades, with particular reference to viral epidemics, require innovative approaches for a better clarification of their origin (Levins & Lewontin 1985). In our opinion, what would be needed today to broaden the horizon of

biomedical research is the recovery of a relationship with the natural sciences, in particular ecology.

As was unequivocally documented by the seminal work by Vitousek and colleagues (1997), we live in a 'human-dominated planet'. Over the past century, humanity has altered ecosystems more rapidly and extensively than in any other comparable time period in the past 12,000 years (UNEP 2005). The physical and chemical matrices of the planet have been modified, triggering deleterious alterations of the biosphere and accelerating a dangerous degradation of landscapes everywhere. The disturbance produced by our action on the natural environment has also significantly impacted on our health. Unfortunately, the effects of these processes over time are not easy to foresee, and they cast a shadow on our future (UNEP 2005).

Meanwhile, like any other component of the ecosystems, viruses have not remained insensitive to this transition and it is reasonable to assume that any newly emerging viral disease represents a new form of 'viral life' shaped by new environmental pressures (Modonesi 2020).

It should be noted that emerging viral diseases are mainly caused by RNA viruses whose transmission cycles involve interaction with ecological factors and evolutionary dynamics (Susser & Susser 1996). For a long time, epidemiological and biomedical sciences have neglected the eco-evolutionary nature of communicable diseases. All the epidemics of recent decades, as well as the pandemic triggered by the spread of SARS-CoV-2, remind us that our unequal relationship with the biosphere raises many troubling challenges that health systems around the world will face in the decades to come (Vitousek *et al.* 1997).

1. A Multifaceted Interaction

Within the natural world, associations between living beings can involve whole organisms or parts of them, such as cells, genes and genomes. For example, viruses usually exchange genes with their hosts: they receive foreign genes that integrate into their own genome and release their genes into the host's genome. This type of association, based on horizontal gene transfer (Burmeister 2015), is quite frequent and represents a widespread phenomenon both in aquatic and terrestrial biotopes. In light of this evidence, the coexistence and mutual interaction between humans and viruses can be described as an ancient and exemplary case of a symbiotic relationship among the many that can be found in nature.

As we will see below with regard to retroviruses, symbiotic phenomena are often characterized by horizontal gene transfer, highlighting that the so-called 'acquired genetic inheritance' provides an important contribution to non-Darwinian (Lamarckian) evolutionary processes.

Viruses interact with organisms from all the three domains of cellular life (*Bacteria*, *Archaea*, and *Eucarya*). However, the uncertain nature and origin of these infectious agents do not allow researchers to place them into an appropriate and definitive position within the tree of life (Moreira & Lopez-Garcia 2009). As a consequence, the scientific community raised many doubts about the legitimacy of considering viruses as 'living entities'. Furthermore, their complete inability to reproduce without exploiting a host cell (Lopez-Garcia 2012) explains why this topic still fuels a lively debate even among philosophers of science (Koonin & Starokadomskyy 2016).

Despite the conflicting conclusions expressed by researchers about the nature of viral particles, it is commonly accepted that viruses have influenced the evolution of a large number of unicellular and multicellular organisms, including our own species (Van Blerkom 2003). Phylogenetic analyses suggest that RNA viruses infecting vertebrates tend to broadly follow the evolutionary history of their animal hosts for hundreds of millions of years (Shi *et al.* 2015). In some ways, this is also consistent with the remarkable spread of retroviruses among modern vertebrates, which supports the hypothesis that their emergence dates back to around 450 million years ago. In other words, retroviruses could be contemporary infectious agents of the first vertebrates that appeared in the oceans of the Ordovician period (Paleozoic era) (Aiewsakun & Katzourakis 2017). Figure 1 gives very interesting hints on the evolutionary process and allows putting some fascinating hypotheses on the role of contingent events like epidemics in animal evolution. We can safely state that viruses are an integral part of natural history and not only a 'threat'. However, we must keep in mind that we are talking about 'deep history', i.e. extremely long periods of time.

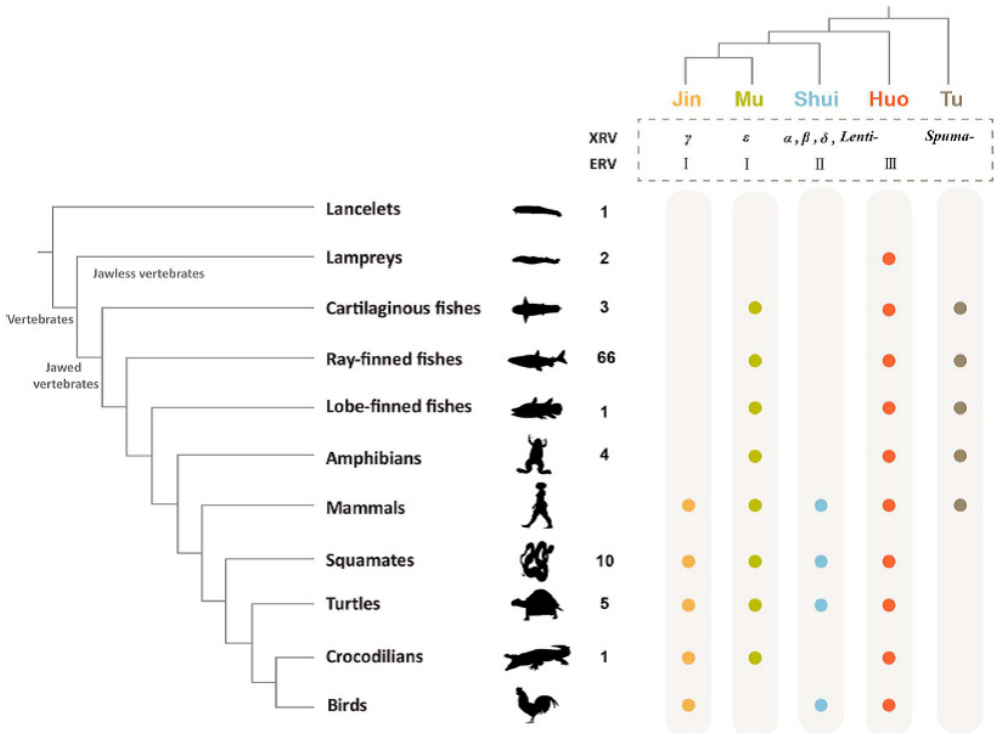

Figure 1: Distribution of the major retroviral clades along different vertebrates. Endogenous retroviruses of vertebrates illuminate diversity and deep history of retroviruses. (From Xu *et al.* 2018).

2. Symbiosis: Ecology of an Evolutionary Strategy

It has recently been estimated that a significant percentage of the DNA sequences detected in the human genome have a retroviral origin or derive from transposable elements (Gonzalez-Cao *et al.* 2016). Although hereditary symbiosis is still considered a rare phenomenon—'the quirk side of evolution', as Stephen Jay Gould put it (1977)—its frequency increases significantly when dealing with viruses and microorganisms. It is no coincidence that physicists interested in the cooperative dynamics of biological systems have coined the term 'collectivist revolution in evolution' to indicate the ecological processes that lead organisms to overcome genetic barriers between species (Buchanan 2009). In general, the symbiotic associations between different organisms are quite variable in the type of interaction and the biological effects on the partners involved. The association can be mutualistic (both partners benefit from the association), commensalistic (one partner benefits and the other remains unharmed) or parasitic (one partner benefits and the other is damaged) (Douglas 1994). A well-known example of mutualistic association is illustrated by lichens. With over 15,000 species, lichens are a successful partnership between a fungus and an algal or cyanobacterial species, or sometimes both. The fungus usually accounts for 90-95% of the lichen biomass and encloses the cells of the photosynthetic symbiont within a network of filaments. The fungus provides a robust structure, while algae and cyanobacteria contribute to the products of photosynthesis and to the fixation of atmospheric nitrogen (Douglas 1994).

However, the data picture of many ecological associations is still poor and unclear. Therefore, these associations do not fall into any of the aforementioned categories. Furthermore, the dynamic interaction established between two partners of a symbiotic relationship may change over time. Defining a continuum along a dynamic path that ranges between competition and cooperation (Dimijian 2000), as shown in Figure 2, could be a good solution to avoid wrong classifications.

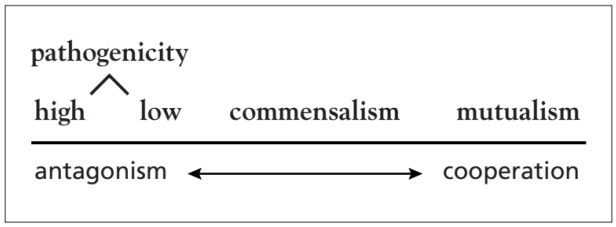

Figure 2: A continuum can be visualized between antagonistic and cooperative symbiotic relationships. Exact assignment of roles is usually difficult and reflects our incomplete understanding of most symbiotic relationships. (From Dimijian 2000).

It is worth noting that many viruses establish a positive or otherwise non-negative interaction with humans. The beneficial effects for the host range from a mutualistic relationship, in which its survival depends on the virus, to advantages that occur only in certain environmental conditions. However, the host/virus relationship can change gradually or abruptly, mainly due to external (environmental) interferences. Often the nature of these interactions, which are probably quite ancient, is clearly symbiogenic (Dimijian 2000). The adjective 'symbiogenic' comes from the neologism 'symbiogenesis' coined by the Russian biologist Konstantin Sergeevich Mereschkowski (1910) at the beginning of the 20th century. Symbiogenesis refers to a close association between different organisms due to ecological events, leading to molecular, morphological and functional changes. According to Mereschkowski, cell organelles such as mitochondria and chloroplasts are the descendants of bacteria that evolved in symbiosis within other cellular organisms. His ideas were updated by the modern 'theory of 'endosymbiotic origin of eukaryotic cell', developed by the American evolutionary biologist Lynn Margulis, which is widely accepted today (Margulis & Sagan 2002; Sapp *et al.* 2002).

It can be assumed that a significant variety of ecological relationships based on symbiogenic processes involved viruses, playing an important role in the origin and evolution of life (Roossinck, 2008). This opportunity that emerged during the natural history of living beings must have favored the emergence of new biological systems generated by the integration of creatures phylogenetically unrelated to each other, giving rise to a non-trivial and unconventional form of evolution referred to as 'reticulate evolution' (Carrapiço 2010; Gontier 2015). Reticulate evolution is a concept that accounts for the evolutionary change induced by mechanisms and processes of symbiogenesis, lateral gene transfer, hybridization and infectious inheritance (Carrapiço 2010; Gontier 2015). According to that interpretation, each emerging evolutionary entity possesses biological traits that go far beyond the sum of the individual properties of each original partner triggering the development of an integrated whole with innovative attributes. In this process, the new organism, or superorganism, develops functions and synergies that are not detectable in the individual species from which it was formed (Carrapiço 2010). The result can be viewed in Figure 3.

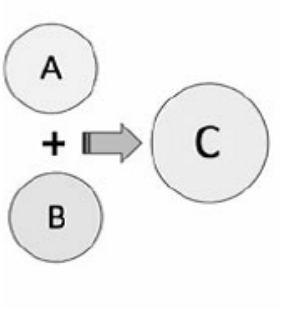

Figure 3: The new entities formed by the integration of two individual organisms (From Carrapiço 2010).

3. Very long and very short time scales

As mentioned before, the interaction between viruses and multi-cellular organisms has a very long and fascinating history and, like all the very long histories, is made of both light and dark. A paradigmatic case are the previously mentioned retroviruses which, by their peculiarity of having RNA as genetic material and their ability to integrate into host DNA by retro-transcription, allow us to keep track of ancient infections by the detection of retroviral sequences embedded in human and animal genome. Endogenous retrovirus sequences (ERVs) represent a genetic legacy due to ancestral integration of exogenous retroviral agents into the genetic makeup of mammals and other vertebrates (Feschotte & Gilbert 2012).

Once the genome of cells that give rise to gametes (eggs and sperms) has been colonized by viral sequences, copies of the pro-viral DNA can be further amplified due to germ-line re-infection events (Dewannieux *et al.* 2013). These sequences are ubiquitous in vertebrates, and in human genome account for around 8% of the genetic material (so largely outnumbering protein-coding genes) (Xu *et al.* 2018). These sequences, for the most part, belong to the group of long-terminal repeats (LTRs) which also include the mammalian apparent LTR retro-transposons. Just like structural genes, ERVs undergo epigenetic regulation by histone methylation/demethylation and have a tissue specific expression level. Moreover, they have a much greater tissue specificity than structural genes, so that we can obtain a more accurate discrimination of different cell populations by means of ERVs than with other genes (Tokuyama *et al.* 2018). This implies that they are now an integral part of our genetic makeup. Indeed, the lack of specific ERVs prevents the development of the embryo and also the maintenance of the organization of complex tissues depends on the ERVs (Fu *et al.* 2018; Liu *et al.* 2019).

	HERV-K	HERV-E	HERV-W	HERV-H	HEMO	HERV-FRD	HERV-R	HERV-P
Breast	X		X	X	X		X	X
Lymphoma	X		X	X				
Leukaemia	X						X	
Endometrial	X	X	X			X	X	
Prostate	X							
Seminoma	X		X					
TCC			X					
Ovarian	X	X			X		X	
Melanoma	X							
Lung	X			X	X		X	X
Colon	X		X	X				X
Pancreas	X							
Sarcoma	X							
Urothelial/Renal	X	X	X	X	X		X	
HNSCC	X						X	

Table 1: Overview of the human ERVs detected in several cancers. The lack of X only means that there is no record of the human expression of that ERV for that cancer, and not necessarily that it is not present. (From Bermejo *et al.* 2020).

This as for the 'sunny side': the above-sketched interactions describe the establishment of an unavoidable vital link between the expression of genes due to very ancient viral infections and human life. On the other hand, the 'dark side' concerns the involvement of ERVs in cancer and auto-immune diseases, that in turn are both 'tissue-based' pathologies and in a sense can be considered as the price we have to pay for being complex and very finely integrated organisms. Although the tumor mechanisms induced by ERVs have not yet been fully elucidated, the role of their sequences in the transformation of normal tissues into neoplastic tissues is widely recognized. Investigations of the past few decades suggest a broad association of different human ERVs with several cancers (Bermejo *et al.* 2020) (Table 1 above).

Let's now shift to a much shorter time scale and give a look at Figure 4. The exponential increase of epidemics episodes very clear starting from the Seventies, goes hand in hand with globalization processes to be intended as both destruction of former wild areas with a consequent increase of zoonotic infections passing by animals to humans and the unprecedented connectivity linking very far away areas. If and when these episodes, on the long run, will end up into mutualistic interactions is totally out of reach of our predictive ability. We can (and must) only focus on the rising menace of recurrent pandemics caused by a very recent ecological disaster.

Despite the substantial scientific attention that viruses rise due to their pathological outcomes in humans, animals and plants, a broader and more realistic vision has emerged in recent decades

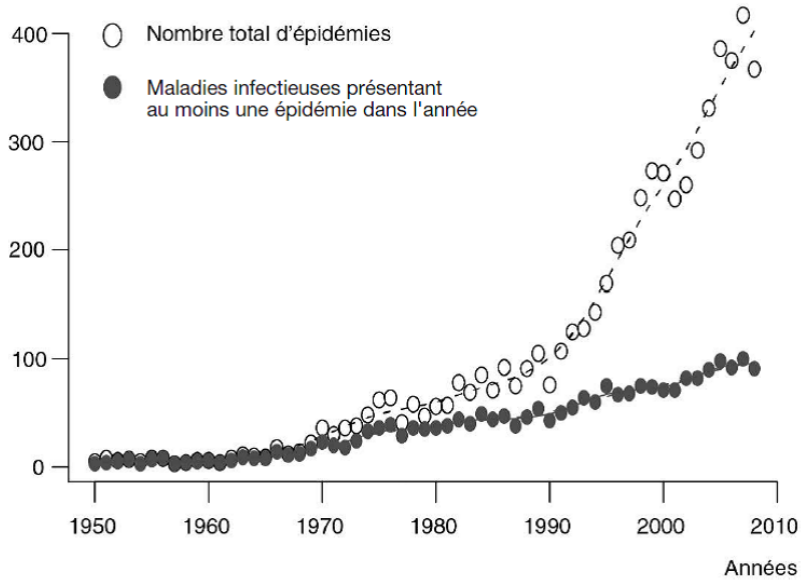

Figure 4: Evolution of the number of infectious disease epidemics in the world from 1950 to 2010 (from Morand & Figuié 2016).

that emphasizes the key role they play within the biosphere. This more comprehensive knowledge about viruses suggests that a different conceptual approach is needed in biomedical investigation of emerging viral pathologies. We should focus on the integration of epidemiological and ecological data in order to clarify what happens in the early stages of emerging viral epidemics. This would allow researchers to have a more complete range of information useful for studying the dynamics occurring at the host-pathogen interface. It is important to underline that in man-made environments such as urban, rural and industrial areas, the risk to public health due to the spread of an emerging pathogenic virus also depends on the population density, people's lifestyles and human mobility, as well as on social and economic factors together with the reactivity of political and health institutions. More succinctly, we call all these elements 'human ecology', giving this term a much more inclusive meaning than its common usage. Human ecology is the complex of biological, cultural, spiritual, social and political characteristics that allow us to define a profile of the relationship that each human population establishes with the environmental context. The intertwining of these elements designates the background affecting the behavior of a viral disease, showing its epidemiological, biological and clinical traits.

4. The relevance of time and space

Since the mid-20th century, ecological and evolutionary processes have been recognized as key factors in promoting the emergence of new viruses and the re-emergence of older ones. In the early 1950s, a 'systemic' look at infectious diseases was developed taking into account two important requirements for the health of human populations: their historical (evolution) and spatial (ecology) properties (Arrizabalaga 2018).

Starting from the concept of 'bio-cenosis', which refers to the complex of all living organisms that co-evolve and interact within a given territory, the term 'patho-cenosis' was coined to indicate a well defined set of pathological states of a population. According to such an approach, the frequency and distribution of each infectious disease depend not only on biological and environmental factors (i.e. pathogen, virulence, reservoir species, climate, degree of anthropization, and so on) but also on the frequency and distribution of all other diseases within the same population (Grmek 1997). A paradigmatic example is provided by the plague, which spread across Europe after the decline of leprosy between the 12th and 14th centuries and was followed by other infectious diseases in later times (Weiss & McMichael 2004). The so-called 'black death' influenced the pattern of transmission and distribution of other pathogens associated with human population density. The plague likely engaged a strong competition with other contemporary pathogens such as smallpox and measles. In turn, the smallpox and measles viruses were present in Europe well before the arrival of *Yersinia pestis*, which blocked their progression, and they only re-emerged around the 18th century when the plague had disappeared from Europe (Barquet and Domingo 1997; Hopkins 2002). The modern temporal and spatial reconstruction of the plague has had a significant weight in the history of biomedical sciences, because it has broadened the narrow mono-disciplinary perception of diseases as isolated entities. In the investigation of the events underlying the onset of infectious diseases, an integrated approach was proposed aimed at giving a more realistic weight to temporal and spatial factors and their mutual interaction. Since then, the health condition of a population has been conceived as a dynamic process influenced by a wide range of factors often neglected even by the most advanced epidemiological studies. It can be argued that in most cases both the appearance and the re-appearance of new and old viral epidemics depend on ecological, evolutionary and social processes and cannot be considered as mere accidental events. Revisiting the history of diseases from such an integrated perspective, namely taking into account the social and environmental contexts as well as the concomitance of other pathogens in the population, allows us to glimpse a logic in the sequences of events.

5. Are there any good viruses?

An important aspect of viruses concerns their ability to implement population dynamics very similar to the ecological behavior of unicellular and multicellular organisms. Nickbakhsh and colleagues (2019) have argued that positive and negative interactions between flu and non-flu viruses at the population level occur in

the respiratory system of human hosts. In other words, when multiple pathogens have infected the same host organism, a competitive or cooperative interaction can arise. Interestingly, many cases of viral infections showing beneficial effects on human and animal hosts were investigated. Sometimes, the available data does not allow researchers to understand the mechanisms underlying these mutualistic interactions. For example, protective viruses often interfere with various biological functions of the pathogenic viruses, including their replication. In other circumstances protective viruses modulate the host's reaction by stimulating innate immunity (Barton *et al.* 2007). As can be guessed from the examples briefly reported below, this area of research has so far been poorly considered, but it deserves much more attention (Shen 2009).

Some long-term studies have shown that people infected with HIV-1 develop full-blown AIDS much more slowly if they are also infected with the *hepatitis G* virus, a virus that is fairly common in humans (Heringlake *et al.* 1998; Tillmann *et al.* 2001). Two other interesting cases concern human cytomegalovirus infection, which is involved in the suppression of HIV 1 superinfection, and *hepatitis A* virus, which can suppress infection with *hepatitis C* virus (Deterding *et al.* 2006; Shen 2009). Parato and colleagues (2005) showed that several oncolytic viruses can attack neoplastic tissues exerting a protective action on the host. In an experimental setting, rodents infected with murine gammaherpesvirus 68 (analogous to the human pathogenic Epstein-Barr virus), or with murine cytomegalovirus (related to human cytomegalovirus), have been shown to be protected from infection by both *Listeria monocytogenes* (responsible for foodborne infections in humans) and *Yersinia pestis* (the agent of the plague) (Barton *et al.* 2007). Another experimental study found that viruses can also protect against metabolic diseases. For example, mice prone to developing type 1 diabetes were found to be protected from the metabolic disorder when infected with lymphotropic viruses (Oldstone 1988).

Conclusions

An important issue mentioned above concerns the anthropization of a territory, the degree of which can be assessed by using different types of variables and indicators. In purely ecological terms, anthropization is the conversion of natural spaces and landscapes by human action. While in classical ecological thought anthropization has substantially to do with various forms of environmental degradation, a broader and more realistic conception of 'anthropized environment' also embraces less obvious aspects such as privatization, commodification and artificialization of environmental contexts and resources.

From a historical and anthropological point of view, it could be argued that whenever human societies encountered a survival problem or a limiting factor, they used their creativity to shape resources and territories and make them as consistent as possible with their own needs, such as in the case of the selection of plants, the domestication of animals, the regulation of waterways, the terracing of slopes, urban development and transport networks.

Today, however, in many cases anthropization is mostly indirect and conditioned by financial and economic speculation as well as by the use of invasive technologies.

The impressive deforestation of huge territories of the world represents perhaps the most dramatic and emblematic case of anthropization, even beyond the beneficial effects that these natural environments have on climate regulation.

A sort of 'Promethean' vision of the nature/society relationship has now been strengthened, starting from the assumption that, with the help of science, humanity will free itself from the constraints of nature in achieving the true human freedom.

Even in terms of public health, such an ideology can be very dangerous. Globally, natural forests cover around 4,000 million hectares (ha), corresponding to 30% of the Earth's surface. The world is losing its forests at an alarming rate of over 3 million hectares per year. Over a quarter of the reduction in forest habitats is due to the deforestation of large areas to make way for permanent crops for the production of commodities (IPBES 2019).

Deforesting means losing biodiversity, that is to say the key factors in the emergence of zoonotic diseases. According to recent data, about 75% of the Earth's terrestrial environment has been severely altered by aggressive economic activities. When natural habitats are transformed and replaced with artificial environments, the risk of infectious disease outbreaks increases.

Deforestation exposes humans and livestock to the spread of zoonotic pathogens. These interactions increase the likelihood that animal viruses can jump from reservoir species to our species (IPBES 2019).

The interstitial pneumonia (COVID-19) outbreak caused by Sars-CoV-2, first detected in Wuhan, China during the second half of 2019 must be seen as a loud and clear alarm coming from the global ecosystem.

To conclude, it is difficult to assess the impact of SARS-CoV-2 pandemic in promoting the integrated approach outlined above. Again, we see both a light and a dark side. The positive side depends on a marked interest in zoonotic viral infections and their mode of transmission through intermediate species. Attention to environmental problems could highlight a growing tendency to enhance prevention strategies based on our relationship with ecosystems. The dark side is very evident in terms of both a deep cultural crisis of science made clear by the extreme fragmentation of competences exhibited by scientific community and a predominant economic interest aimed exclusively at cure (in the form of vaccination) of specific epidemic events. Such an approach is undoubtedly more consistent with the prevailing economic order, but it is also far less effective than serious preventive strategies.

The struggle for a broader perspective that translates into interdisciplinary research and concrete policy acts (we are full of environmental chatter with no practical consequences) suggests that the systemic approach we are advocating here, is at this time, mandatory.

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Opinion

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The Concept of Nature between Heraclitus and Prigogine

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Abstract

In the Greek tradition, "physis" denotes both the "nature" (the "essence") of an entity and its accomplishment, that is to say, its "development". For example, the embryo is the "essence" of the unfolding organism and, at the same time, the process leading to it. The egg is a symbol of wholeness, but this totality cannot be perceived out of its self-organizing process. In this way, according to Heraclitus, the living being "hides." Essentially, the Self can only be recognized as an outcome rather than a starting point. This stance, endorsed by Heraclitus and Aristotle, has been left aside by modern scientific research since Bacon's time when the less noble Stoic inheritance was tacitly assumed. In Stoics' belief, *physis* means power (God or otherwise), i.e. the causal principle (*causa prima*), which is involved in generating any natural process. Having emphasized the "cause"—even in absence of a clear definition of such a concept—the "real process" lost its relevance and its intelligibility was impaired. The description of the process began to be confused with the description of the "entity" (the thing-in-itself), and this representation eventually ended up identifying the "essence" with its (presumed) "primary" causes. This way, natural things and/or processes were re-absorbed into their presumptive causes, missing the true complexity of the natural system.

Keywords: nature, Heraclitus, Aristotle, self-organization, complexity, development

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1. The Concept of Nature after Laplace

The development of physics-chemistry over the last 30 years—followed in its footsteps by a more recent revolution in biology—has radically changed the worldview handed down by Newton (Prigogine & Stengers 1979).

A probabilistic representation has recently challenged the idea that nature may be predictable and exhaustively described through deterministic laws. This new view includes the "arrow of time" between its variables and tries to explain how, far from equilibrium, non-linear dynamic processes originate new emerging structures and, eventually, new order's form.

Indeed, the deterministic approach cannot explain a multitude of phenomena accumulated over the centuries. The amount of "unexpected" and "contradictory" results have led to a radical critique of the dominant paradigm, limiting the validity of Newtonian physics within a well-specified level of observation and narrow areas of phenomena where processes can "reasonably" be considered linear processes (or transformed into linear processes, i.e. "linearized"). There is no doubt that classical science cannot solve problems involving complex systems. This holds true even when only well-defined deterministic forces are at play in the system (e.g. the Three-Body Problem addressed by Poincaré). However, it becomes blatant in areas characterized by

even greater complexity, like embryonic development, or in the genesis of multi-factorial diseases, such as cancer. This aspect deserves to be deepened. Indeed, embryonic development is a well-ordered phenomenon (despite teratogenesis is always a possibility), where many non-linear processes intertwine. The paradox lies on the fact that a complex, non-linear ensemble of dynamical processes—which are dramatically affected even by very small fluctuations in the environmental conditions—almost invariably leads to a foreseeable, well determined, yet non-deterministic outcome. Classical physics and a positivistic approach are unable to accommodate such a bewildering issue, especially when addressing it (as it often happens) in terms of "control" and "cause and effect."

Since Francis Bacon, science has shown a marked (though not exhaustive) tendency to identify the "understanding of nature" with the "control of nature". Without a doubt, the framework of natural processes within models of deterministic and predictable rules, has laid the basis for such a control. Possibly, the confusion arises when the "mechanistic" and the "system" explanations mix: understanding a "molecular mechanism" does not imply that we can capture the "logic" behind an organism (Koutroufinis 2017, pp. 31–37; Koutroufinis 2020, pp. 261–266). Certainly, nature does not care about our models and our attempts to make it predictable. Even linear processes are far from equilibrium. They are subject to unforeseeable developments and affordable only in terms of *probabilities*.

The physics of the past centuries has evolved. It now recognizes that nature is neither "simple" nor able to be explained through a few equations entangled within a "theory of everything." Complexity is an intrinsic feature of nature and requires new methodological and analytical tools.

Newtonian physics posits that the structure of dissipative structures (i.e. open thermodynamics systems) grow disorganized while evolving over time as the system's entropy increases. Thus, a temperature gradient in an isolated system will inevitably efface any difference and lead to equilibrium. The thermodynamics of equilibrium teaches that the process "naturally" tends toward disorganization, evolving into a growing and irreversible disorder. In reality, the vast majority of phenomena does not happen in isolated systems and takes place in conditions that are far from equilibrium. New structures arise precisely from these situations. Rather than leading to a chaotic state, dissipative processes thus originate new forms of order. The equations describing complex systems involve multiple solutions. It is, therefore, impossible to predict the solution that the system will choose. This mechanism underlies the hidden creative power of nature. As Ilya Prigogine pointed out, "as soon as a system departs from equilibrium, automatically, whatever the initial conditions are, complexity appears [...] the non-equilibrium is the source of complexity" (Prigogine & Benkirane 2002, p. 44).

Within equilibrium boundaries, matter is "blind", repetitive, and always equal to itself. Matter far from equilibrium faces a wide variety of situations. It travels through a succession of bifurcations that mark the "history" of the system from a given point: the breaking of symmetry. From such a moment, the system can "sense" the time's flow. We can then recognize "a before" and "an after." Nature can be grasped only as a process, a long narrative, during which it creates and destroys, inventing new solutions. The unpredictable cannot be excluded from the intelligibility of *physis* (Stewart 1989).

The *Age of Enlightenment* prioritized the "being" in opposition to the "development," therefore, binding rationality in the (narrow) realm of determinism and certainty. However, it is increasingly clear that the "becoming" rather than the "being" is essential from an ontological perspective. In other words, there can be no scientific understanding beyond the "history" of a system.

It is remarkable to consider how this modern scientific vision of the world overlaps with the ancient Greek worldview and, more generally, the traditional concept of nature.

2. Heraclitus' aphorism

For Heraclitus, "*physis kryptesthai philei*", namely: "Nature loves [tends] to hide." Somehow, this is the sense that, especially since the Renaissance, had become uncritically dominant until P. Hadot reworded it in such a convincing and very different reading (Hadot 2004). According to the Greek view, at once, "*Physis*" denotes both "nature" as the "essence" of any entity, and its accomplishment, i.e. its development. The embryo offers a meaningful example: it is the "essence"

of the becoming organism and, at the same time, the process leading to it. Furthermore, in alchemy, the egg is a symbol of wholeness, the seed from which the world develops. The egg symbolizes the periodic renewal of nature and signifies how life is born from death: this assumption explains why an egg represents the "secret meaning" of Easter (Chevalier & Gheerbrant 1986). Notwithstanding, this cannot be totally perceived out of the time in which it becomes *self-organized*. Time must be considered akin to a key-dynamic parameter, and it drives the system toward "unexpected" issues. Moreover, identity can only be recognized as an outcome rather than a starting point.

According to the widely known interpretation in reference to the previous statement, "nature loves to hide" and, as Einstein pointed out, "nature hides her secret because of her essential loftiness, but not by means of ruse" ("*Die Natur verbirgt ihr Geheimnis durch die Erhabenheit ihres Wesens, aber nicht durch List*," as quoted by Pais 1982). This is the mainstream meaning, especially since the end of the Renaissance.

Heraclitus himself provided some useful tracks to better identify the hidden meaning of an aphorism, which was otherwise destined to multiple interpretations. He outlined, "*physis* is the process of mixing things that unite and divide." Hadot showed that even more well-based interpretations may be proposed, such as: "nature is what gives birth and kills" and "nature is what makes things appear and disappear." These must be considered with the following Heraclitean statements: "form tends to disappear" and "what is born tends to die." In other words, there is no *physis* outside of time. Sophocles rightly argued:

> The vast, countless time first draws [phuei] things that were not apparent and then buries [kryptetai] things that had appeared (Sophocles, Ajax, vv. 646 ff).

Time in Newtonian physics is an inert support of reversible processes whose "arrow of time" is irrelevant. This is not the time referred to by Sophocles. On the contrary, traditional thoughts on nature conceived time as a fundamental property in shaping natural things. "Everything mixes within the game of the *aion* [the time]" wrote Lucian of Samosata in his *Philospher for sale* (No. 14).

By considering the meaning of this sentence, how can one not think of the complexity of biological pathways of growth, differentiation, and apoptosis? These lead to life through the unfolding of new forms and cyclical phases of programmed death.

Claude Bernard, the father of physiology and forerunner of Systems Biology (Noble 2007) had grasped this paradoxical character when stating:

> There are two types of seemingly opposed life phenomena: the first tend to organic renewal and are somehow hidden; the second are committed to destroy the organic structures (….) These are usually described as the phenomena of life, so that what is named life is essentially death. (Bernard 1872, pp. 327–328, n. 219)

Bernard uses a biological language, but it is easy to see how the process of *emergence* of complexity, as described by Prigogine, shines through his perspective. Like on-equilibrium thermodynamics, the traditional conception of nature shifts the focus from the "essence" toward the "transformation." This tries to grasp the meaning of things in their live "becoming," rather than as isolated entities ("the thing itself"), detached from their environment and time. Most significantly, Marcus Aurelius explains with conciseness:

> Acquire a method of contemplating how all things change into one another. Constantly apply to this part [of philosophy], and exercise yourself thoroughly in it. (Aurelius 2008, p. 124)

Similarly, in his *Diseases* (II, 3, 55), Hippocrates considers *physis* to be the whole organism as shaped by its proper overall development. From the fifth century B.C., according to Plato and Aristotle, *physis* is seen as the formation of something that endeavors to realize its true essence. For both of the above-mentioned philosophers, "nature" is fundamentally an inner principle of change that pushes along a path and leads toward a place (a "state"). The agent recognizes such a place as "natural". Here, "natural" means "proper." The driving force that directs along this state is identified with the "aspiration" toward a "form" on which the natural process tends to be modeled. According to Plato, the divine soul drives such a process. The soul shapes the matter as an artist shapes a work of art. For Aristotle, the developmental

process is immanent to matter: "nature" possesses an intrinsic "outcome" ("entelechy"). Ultimately, this allows for recognizing a true identity: nature becomes what it should be, and the final development is a witness to it. Two millennia later, Marsilio Ficino will add that nature is an art that can shape matter, starting from its inner core (Ficino 1965, Book 4, ch. 1, pp. 239–284). Like an artist who "chooses" the forms, nature selects different forms: the "freedom" to select among different configurations ("forms") provides the fundamentals of "diversity". Nowadays, we would be tempted to say that nature, along its developmental path, selects different states ("attractors") where its trajectories converge. Unfortunately, such a statement left an unanswered question: if Aristotle had assumed that such a selection would occur during the initial states or across the entire developmental path.

Understanding "nature" independently from its proper dynamic context, by which nature becomes "itself," is therefore, impossible. Conclusively, Aristotle points out that "the best method [of investigation] should be to observe how things are born and how they grow" (Aristotle 1999, I, 2:1252a 24).

The aphorisms attributed to Heraclitus—"Everything flows" and "No man ever steps in the same river twice"—clarify how the idea of nature in ancient Greece cannot be separated from the dynamic processes that we observe.

In establishing a parallelism between the emerging of complexity and the artist's work, both Plato and Aristotle seem to give up the cornerstone of the future scientific epistemology, i.e. the certainty of measurement. Epicure and his epigones violently criticized Plato's use of myth in explaining nature. They considered such an approach to be incompatible with the need for scientific certainty (Festugière 1946, pp. 102 ff.). Paradoxically, since Dalton, and then with the advent of quantum physics, it has become increasingly evident that "certainty" is possibly a scientific myth, a modern fairy tale without convincing foundation. Indeed, the quest for "certainty" and "accuracy" has little to do with the intelligibility of the world. Most likely, it is rather meant to satisfy a psychological need, a kind of "infantile obsession," as stigmatized with humor by Robert Laughlin:

> Physical scientists [...] tend to see the matter morally. They orient their lives around the assumption that the world is precise and orderly, and its occasional failure to conform to this vision is a misperception brought about by their not having measured sufficiently accurately or thought sufficiently carefully about the result. This sometimes has bittersweet consequences. (Laughlin 2005, p. 12)

Moreover, a negative consequence of this attitude is "that truth and measurement technology are inextricably linked." Therefore, "exactly what you measure [....] and so forth matter more in the end than the underlying concept" (Ibidem, p. 14).

Laughlin depicts disorder as a characteristic feature of the microscopic world, which is intrinsically uncertain and unpredictable. Unpredictability must be distinguished from noise. Microscopic unpredictability, however, turns into order at higher levels, where complex collective behaviors emerge and couple with environmental constraints. Constraints "canalize" the disordered behavior into a few, well-ordered patterns. This means that "determination" is inevitably associated with a reduction in the degrees of freedom actually available for a system (Bizzarri, Giuliani, Minini, Monti, & Cucina 2020). Conversely, as the process is non-linear and many factors are involved in the morphogenetic process, predictability becomes a statistical property. As such, it does not apply to any molecule, but to the whole. No law can deterministically predict the behavior of individuals. However, the social behavior is likely to be predicted with sufficient reliability. The real mystery is how disorder turns into order when the system shifts from the microscopic to the macroscopic level—*ordo ab chao*, in alchemical terms.

3. The idealization of nature during the Renaissance

The research of the past century does not seem to have received any benefits from this *lectio*. Since the Renaissance, nature has been increasingly considered akin to an immutable reality that must be epitomized and thereby recognized as an ideal entity. After removing time as an intrinsic component of the physical world and as a necessary variable in the scientific description of reality, it eventually became possible to justify a radically different approach that paved the way for a scientific framework (exclusively) rooted on reductionism and determinism.

After forgetting Aristotle (his "*damnatio memoriae*" started with Galileo), modern scientific research has focused on the less noble Stoic inheritance.

In Stoics' belief, *physis* means power (God or otherwise), i.e. the causal principle (*causa prima*), which is involved in generating any natural process. The interpretation provided by Stoic philosophers marks the subtle, yet relevant, transition from the study of the phenomenon ("experience") to the recognition of the power (the "cause") that generated it. Having emphasized the "cause"—even in absence of a clear definition of such a concept—the "real process" lost its relevance and its intelligibility was impaired. The description of the process began to get confused with the description of the "entity" (the thing-in-itself), and this representation eventually ended up identifying the "essence" with its (presumed) "primary" causes. This way, natural things and/or processes were re-absorbed into their presumptive causes, missing the true complexity of the natural system.

In modern times, this was done by identifying the cell or, even worse, the overall organism with the genome: eventually and quite arbitrarily, at the least, all possible "causal powers" have been brought back to the DNA.

The identification of "power" with God or some other principle (*élan vital*, DNA, etc.) has encoded the concept of nature among philosophical categories. This has put the "secrets of nature" into the scenario of the philosophical debate. With time, the decryption of these secrets has become the equivalent of revealing the "divine secrets", as Nature itself has ended up replacing God. Conversely, the difficulty in penetrating these secrets has legitimized the less likely version of Heraclitus, i.e. "Nature loves to hide."

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Books

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Review of Thomas McCabe (ed.) 2021, *Descent and Logic in Biosystematics*. Juneau: Perseverant Publishing

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Review of: Thomas McCabe (ed.) 2021, *Descent and Logic in Biosystematics*. Juneaus: Pereseverant Publishing

Who cares about biological taxonomy these days? To the layperson, a taxonomist belongs to the past and is an eccentric and slightly absent-minded scientist: he goes around the world obtaining biological specimens (preferably insects), transfers them to his laboratory, performs careful analyses, and hopes to find a new species to leave a mark in history. To the average biologist, taxonomy is embedded into a software which, by analyzing the DNA in a sample, will produce 'metagenomics' data (preferably relative to microbiota). Here, the fingerprint sequences act as a kind of barcode for each and every species.

Both the layperson and the average biologist, from two seemingly opposite perspectives, consider taxonomy as a substantially irrelevant activity.

In fact, this is not the case. We could tell the layperson that a great part of animal species (especially insects) is still unknown. Such a "dark biological matter" is abundant in ecologically crucial areas like tropical forests. It severely biases our estimation of biodiversity and, consequently, the estimation of the ecological state of our planet (Monastersky 2014; Hui *et al.* 2008). On the other hand, we could point out to biologists that obtaining consistent results when it comes to underrepresented species is especially hard. We need to shift from a purely ontological (e.g. relative abundance of microbial species in a gut sample) to an ecological appreciation of the entire microbiota in terms of the relative abundance of species with similar metabolism. This then involves a similar ecological value for the microenvironment of the gut (Martino *et al.* 2020).

Books like *Descent and Logic in Biosystematic*s are precious for generating interest among scientists and, more generally, educated readers. This can shed light on the pillar of both medicine and biology, i.e. giving a name to observed entities.

Thomas McCabe is a physician. He introduces his work by establishing a basic difference between medical and biological systematics. In fact, medicine can find concurring diseases and, therefore, a multiple determination in a single specimen. However, biology focuses more on elemental species. Such an interesting starting point allows the author to face the problem in terms of "descent", i.e., genetics. Indeed, McCabe ascribes the fuzziness between the genetic variability of intra- and inter-species (especially for microbes) to genetics.

It is a pity that the author almost completely skipped the long and brilliant tradition of numerical taxonomy, as presented in the crucial work of Sneath & Sokal (1973). Numerical taxonomy has inspired generations of scientists from every discipline. It is

also at the base of the current interest for "species as attractors in phase space" that unites the biological and physical concepts of "species" as a "discrete and recognizable favoured configuration of features" (Kasperski & Kasperska 2021).

This book, which is hard to come by these days, is inspiring and contributes to a necessary cultural resurgence of life sciences. It is available for free at: https://www.perseverantpublishing.com/pdf/Descent_and_Logic_in_Biosystematics_-_McCabe_2021_1.2.1.pdf

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