Advances in Historical Studies, 2024, 13, 122-155
https://www.scirp.org/journal/ahs
ISSN Online: 2327-0446
ISSN Print: 2327-0438

"Centric" and "Excluding" Conceptions of Biological Inheritance

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How to cite this paper: Müller, G. A. (2024). "Centric" and "Excluding" Conceptions of Biological Inheritance. *Advances in Historical Studies, 13,* 122-155.
https://doi.org/10.4236/ahs.2024.132007

Received: February 19, 2024
Accepted: June 23, 2024
Published: June 26, 2024

Abstract

The detection of DNA as the transforming principle in bacteria 95 years ago, almost immediately led to 1) refutation of the old and heavily disputed concept of inheritance of acquired featured, since this would necessitate rewriting of "the book of life" by environmental factors, such as nutrition, stress, and 2) exclusion of the existence of any matter of inheritance different from DNA and genes. In this opinion paper, it is intended to overcome this narrowing by the re-consideration of other cellular constituents, i.e., plasma membranes (PMs) and organelles as well as the previously identified extracellular vesicles (EVs) and micelle-like complexes, which may operate as vehicles of the transfer of so-called M(E)Ls from donor to acceptor cells, from parental to offspring organisms, as non-DNA matter of biological inheritance. M(E)Ls represent arrangements of integral and peripheral membrane proteins, glycosylphosphatidylinositol-anchored proteins (GPI-APs) and cytoskeletal protein components in concert with cholesterol and (glyco)phospholipids into structures of characteristic configuration and topology and function, e.g., blebs, protuberances, invaginations. Recent experimental studies have demonstrated that upon release from donor cells and subsequent transfer to and replication by mechanisms of self-organization (rather than self-assembly) in acceptor cells, those MELs induce novel metabolic phenotypes, such as stimulation of lipid and glycogen synthesis. Most crucial, in rats and humans the structure of MELs is susceptible to environmental factors, such as mechanical distortion, nutrition, which may contribute to phenotypic plasticity and the inheritance of acquired traits. Those epigenetic mechanisms, which are apparently not based on modifications of DNA and DNA-associated proteins, have not been adequately addressed so far in studies on the pathogenesis of common complex diseases. The presented opinion is aimed at the initial encouragement for the identification and characterization of some of the (most important) reasons for the adherence to the "DNA-/gene-centric" conception of biological inheritance for almost a century and the accompanying ongoing exclusion of intercellular and transgenerational transfer of non-DNA matter from the repertoire of (epi)genetic mechanisms for the explanation of phenotypic plasticity and the inheritance of acquired traits. The unraveling of the network of human and non-human actors constituting the apparatuses of the production and observation of the phenomenon of inheritance, including but not restricted to methods (e.g. microscope, centrifuge), materials (e.g. chemicals, cells), documentation (e.g. data bases, journals) should be guided by the following basic questions: a) which actor was involved, b) which method was used, c) which scientific, sociocultural, economic or political motivation was followed, in the course of inclusion/exclusion of DNA/non-DNA matter as the agents (in the broadest meaning) into/from the material-discursive practices of studying of intercellular and transgenerational inheritance. Moreover, the encouragement towards opening for the transfer of both matter, i.e. substance, and information, i.e. form, requires significantly intensified transdisciplinary cooperation between natural and human sciences, in general, and biology (i.e., genetics, molecular biology, and cell biology) and the history of biology and the philosophy of biology (i.e., science and technology studies), in particular, in the future. Crucially, the presented encouragement does and must not lead to simple replacement of the "DNA-/gene-centric" conception for the next "centric" and "excluding" one, e.g., "MEL-centric" one. Rather, it may be helpful to resist the putative (re-)narrowing in the one or the other direction, with far-reaching implications for our societal and political systems, in general, and our healthcare system, in general.

Keywords

Agential Realism, Extracellular Vesicles, Inheritance of Acquired Traits, Membrane Landscapes, Science and Technology Studies

1. Introduction—Darwin's Pangenesis Hypothesis, Inheritance of Acquired Traits and Epigenetics

Charles Darwin developed his Pangenesis hypothesis more than 150 years ago to support his theory of evolution and eventually to adequately explain a variety of biological phenomena, but above all inheritance, species diversity, individual variation and the development of organisms (Darwin, 1868). For this purpose, he introduced molecules of heritability and heredity and called them "Gemmules" (Darwin, 1869, 1871). Pangenesis was based on the idea that all parts of the body produce units, which were able to replicate by self-division, and after being transported to the sexual organs, were instrumental to heredity and development. According to his conception, those units or "Gemmules", which were at the time not clearly distinguishable from cells and could not be easily adjusted to the needs and predictions of cell theory are produced and released by all parts, organs and cells of the organism and then accumulate in or near its germ cells due to mutual affinity, but do not represent a simple image or representation of the parts, organs and cells that have produced them. After transferring from the gametes to the zygote, the parts, organs and cells that were originally responsible for their production and release are formed from the "Gemmules" during development of the zygote to the adult offspring. As a consequence of some ill-defined forces, which may have been characterized during later periods as self-organization and/or self-assembly, the "Gemmules" apparently succeed in the reconstitution of functional parts, organs and cells in the emerging organism, compatible with both preformistic and epigenetic conceptions of development.

Pangenesis allowed Darwin to explain both the frequent and the rare phenomena of inheritance: 1) The assumptions of an equal combination of gemmules, which remained unchanged themselves, between parents, on the one hand, and their superabundance, lack or dormancy, on the other, made it possible to explain blending inheritance as well as what for Darwin were exceptions from this rule as follows: (1a) The concept of dominance, which was not used by Darwin, albeit it had already been introduced by several British horticulturalists in the early 19th century, most prominently by Thomas Andrew Knigth in 1823 (Zirkle, 1951); (1b) the (incorrect) claim that graded characteristics of an offspring were brought about by different numbers of spermatozoa containing different numbers of "Gemmules" (Darwin uncritically accepted results presented by Gärtner (1849) who claimed to have found that even thirty pollen grains did not fertilize a single seed and that at least forty grains were required. Darwin did not cite Nathanael Pringsheim, who in 1855 had shown the penetration of a single spermatozoon into an ovum of the freshwater alga *Vaucheria sessilis* (Orel, 1996: p. 81); (1c) the phenomenon of reversion which was accounted for by the redevelopment of "Gemmules" that had remained dormant. 2) The assumption that "the 'Gemmules' from the modified units will be themselves modified, and, when sufficiently multiplied, will supplant the old 'Gemmules' and be developed into new structures" (Darwin, 1868: p. 390) made it possible to explain the direct action of altered environmental conditions and factors and of the increased use or disuse of bodily parts. With this hypothesis, Darwin finally established the theoretical foundation for a mechanistic explanation of soft of "Lamarckian" version of inheritance of acquired traits.

Despite the apparently discrete nature of the "Gemmules", the fact that an unknown large number of them of all possible sizes, produced during the complete lifespan, accounted for an unknown number of phenomena, blurred any kind of discrete effects and favored the occurrence of quantitative, i.e., infinitesimally small variations. Pangenesis thus supported essential conceptions and claims of Darwin, i.e., blending inheritance, the basic equality between the various forms of reproduction, inheritance of acquired characteristics, the hereditary effects of use and disuse, and small variations. The hypothesis was based in part on dubious and fictitious observations and outdated experimental findings in the fields of fertilization and crossing. It could not serve as a basis for prediction and allowed for arbitrary interpretations. Thus, despite the fact that Pangenesis exhibits features of a modern materialistic theory of heredity, it apparently lacked the characteristics of a testable scientific theory.

Darwin's methodological preferences of quantitative traits and infinitesimally small changes in evolution, his denial of essential differences between modes of reproduction, his adherence to the notion of blending inheritance, despite many cases to the contrary, his assumption that an infinite number of "Gemmules", of all possible sizes, continually produced at all ages, can mix in gradual degrees with others, were strong obstacles to fruitful examination of hereditary regularities or mechanisms. Howard (2009) even considers Darwin's focus on quantitative variation ("infinitesimal small inherited modification") as material for evolution to be the main reason for his not being able to contribute anything relevant to our current understanding of the phenomenon of inheritance. Darwin's preferences point to an underlying basic concept or "theme" (Holton, 1973), that is gradualism. This "theme" together with a not strictly scientific methodology prevalent among natural historians at the time made him adhere to a seemingly outdated and logically questionable, vague concept of heredity, which did not prove fruitful for further research in genetics for more than a century, up to re-consideration and re-acknowledgement of concepts of non-genetic matter.

In fact, up to 1871, Darwin's Pangenesis must be considered as a pure, nevertheless conceivable hypothesis since no experimental efforts for its proof or disproof have been reported at those times (Howard, 2009). But then Francis Galton intended to demonstrate the validity of Pangenesis based on blood transfusion experiments (between rabbits of different coat color). Unexpectedly, he finally failed completely (Galton, 1871). This was possibly due to the experimental design used, as has been suggested more than 80 years later, relying on valid calculations of the putative dilution of the blood of the acceptor animal and seemingly successful efforts of reproduction by some (Sopikov, 1950), but not all researchers involved. Nevertheless, because of Galton's results, Pangenesis was immediately assessed as being completely obsolete. And this view has been kept in the (scientific) communities of geneticists and cell biologists as well as animal and plant breeders for the next period of 70 to 80 years.

Then starting in the early 1950s, the Russian geneticist Sopikov (1954) started in the Soviet Union with his re-investigation of the outcome of blood transfusion on hereditary traits using the blood of Black Australorp roosters and White Leghorn hens, which were subsequently mated with White Leghorn roosters. This experimental protocol resulted in progeny with modified inheritance. Those data on hereditary changes in poultry by blood transfusion were reported to an international audience for the first time by Kushner (1957). In the following years, efforts aimed at the reproduction of the key messages of those blood transfusion, cross-circulation and parabiosis experiments in countries outside the Soviet Union (e.g., France, Switzerland) were performed, which however were based on different animal species and more and less deviating experimental protocols. Not surprisingly, the outcome of these investigations was mixed, with some of them, in fact the majority in number, demonstrating heritable phenotypic changes in the course of blood transfer of either type (e.g., Stroun et al., 1963), whereas others failed (e.g., Kosin & Kato, 1963; Leroy & Benoit, 1963; Lowe et al., 1968). Recently, Yongsheng Liu did a formidable job in analyzing 50 reports about heritable effects of blood transfusion, cross-circulation and parabiosis experiments, ranging from 1950 to up to 1979 (Liu, 2008). He found that 45 of those yielded experimental evidence for animal vegetative hybridization by blood transfer and concluded that this body of experimental evidence cannot be disregarded simply because several scientists had obtained negative results.

In parallel to this line of research on the induction of inheritable phenotypic traits by blood transfer, i.e., during the transfer of some matter in blood (of unknown molecular nature) from donor to acceptor organisms, another independent line was devoted to the unequivocal demonstration of this possibility at the level of expression of an environmentally induced phenotype in parental organisms and its inheritance in their children, despite restoration of the original environment. However, those experiments, which did not consider putative underlying molecular mechanisms, and apparently did not rely on mere adaptive responses, but possibly on acquisition of heritable traits by the parental organism in response to certain environmental cues and their transfer to and maintenance in the offspring organism even in the absence of these stimuli, were as heavily and controversially debated as those of blood transfer.

Unfortunately, the corresponding scientific discourse was overshadowed by the scandals provoked by the famous Austrian zoologist Paul Kammerer in the 1920s and the Russian geneticist Trofim Denissowitsch Lyssenko from 1930 to 1960. Both claimed the unambiguous demonstration of the inheritance of acquired features in vertebrates. Kammerer, for instance, reported the formation of heritable "Haft" or "Brunftschwielen" at the claws of *Alytes obstetricans* if shifted from the typical dry hot to an unnatural wet slippery environment or the mutual alteration of the skin color of *Salamandra maculosa* and *Salamandra atra* if shifted to the typical conditions of life of the latter and former, respectively (Kammerer, 1907a, 1907b, 1908, 1909). Lyssenko postulated the mutual interconversion of wheat and rye in course of exposure to the appropriate environmental conditions, such as cold shock (Lyssenko, 1951 & 1958). Whereas the data provided by Lyssenko and coworkers were subsequently unambiguously identified as fraudulent and fabricated for reasons of ideology and politics (Medwedjew, 1969; Li & Liu, 2010), the fair interpretation of Kammerer's results turned out to be much more controversial and difficult. On the one hand, manipulated specimen of the midwife toad were detected in his lab during an unannounced inspection. On the other hand, it has recently been argued that the results of Kammerer may be explained by the findings of modern epigenetics (Vargas, 2009). This raises the possibility that Kammerer did not alter fraudulently his experiments.

In fact, as early as in the 1930s till present times, a number of findings have been published that can only be adequately explained by the inheritance of acquired traits by non-genetic mechanisms, or *vice versa* that certain "like-from-like" phenomena between parents and their offspring cannot be explained adequately by genetic inheritance. For instance, horse breeders have noticed a long time ago that the foals of large mares grow faster than those of small mares (Walton & Hammond, 1938). Since this effect was independent of the height of the fathers, a purely genetic inheritance was considered to be unlikely. Furthermore, it has been observed that eaten specimens of field radish (*Raphanus rephanistrum*) produce offspring that contain more bitter mustard oil glycosides and are therefore inedible for herbivores (Agrawal et al., 1999). Also, it has been demonstrated that mothers of water fleas (*Daphnia cucullata*) produce offspring that display structures for effective defense, such as large helmets and spines, if living in environments with many predatory mosquito larvae (Agrawal et al., 1999). However, it was only with the methodological and technological advances of recent decades that the molecular mechanisms underlying non-genetic inheritance or phenotypic plasticity (West-Eberhard, 1989, 2008) are going to be understood (Landman, 2022), including those that cannot be traced back to epigenetic processes.

Importantly, for some researchers epigenetic inheritance involves only cellular transmission. Jaan Valsiner (2014) argues that epigenetic theories show that both stability and alteration of biological functions act at different levels. He would like to restrict the epigenetic subject areas to the individual cell, its relationship to its environment (e.g., to other cells) and its integration into different organ systems. Concomitantly, another aspect that is not uniformly understood by epigenetic researchers is thus addressed, the different conception and use of the term "environment". It can mean (body-)external and social as well as (body-)internal and cellular environmental influences and factors. Sara Shostak and Margot Moinester (2015) have pointed to this additional ambiguity: *Scientists conceptualize and operationalize, the environment' in their research in tremendously varied ways. Even within the life sciences, the environment may refer to the cell (the environment of the gene), endogenous hormonal profiles (the environment of the cells), indoor or outdoor ambient environments (the environments of the human body), social networks, poverty, and/or stressful life situations (the social environment); individual behaviors, such as diet and exercise, may also be included in definitions of "the environment*".

The comprehensive and ambiguous application of the term "environment" in epigenetics is also related to the interplay of nature and culture, which emerges and is investigated in a wide variety of binary distinctions, such as gene-environment, biology-sociology, body interior-body exterior, predisposition-nurture. Many researchers see great potential in (environmental) epigenetic studies for a rethinking of reductionistic and (gene) deterministic conceptions towards anti-dualistic and holistic explanatory patterns. At the same time, many researchers produce critical analyses and point out various problems that must first be solved and make it necessary to broaden the view. Lisa Weasel (2016) emphasizes: *Although what might be called the "weak" epigenetic program tinkers only slightly with the reductionistic genomic paradigm, asserting that epigenetic "marks" atop the fixed genome merely fine-tune its singular expression, on a deeper level, a stronger version of the science of epigenetics holds more revolutionary implications for re-imaging the relationship entwinded and emerging out of nature-cultures, and the political potentials of such.*

Against the background of a predominant gene determinism and the "DNA-centric" conception of inheritance, the question arises again and again whether epigenetics manages to refrain from this, since here the environmental influence on gene regulation represents the focus of interest. To present some representative answers, Sebastian Schuol (2016) diagnoses covert gene determinism, while David Moore (2017) speaks of epigenetic determinism. Other researchers also concluded that, despite its openings, epigenetic research does not (completely) get rid of the differentiation between nature and culture, nor of the deterministic logics of development, nor of the "DNA-centric" conception of the inheritance process. Certainly, in the epigenetic discourse, the focus is no longer on the gene exclusively, but rather on complex processes that also take place and have an influence on development and health. Nevertheless, this heterogeneous field is mostly in the tradition of reductionistic experimental strategy and "DNA-centric" narrowing. And so deterministic and "DNA-centric" arguments can often be found in epigenetic studies on inheritance as stated by Waggoner and Uller (2015). Accordingly, epigenetics, in general, remains stuck in traditional scientific concepts and does strengthen the "DNA-centric" conception of inheritance, at least in part.

As already mentioned, "programming" is a common term in epigenetics and can already be found in Waddington (1968). The idea that molecular biological processes take place as programs has now found its way into many areas of modern biology, including the current epigenetic research, as Müller and coworkers commented (Müller et al., 2017): *The metaphor of "programming", which is misleading in that it implies that the phenotypic outcome is determined by a programme, rather than being affected by a range of environmental factors over a sustained period.* They criticize the fact that by assigning the process of programming to organisms, these are understood in such a way that something is called up or switched on in them and then runs according to a predetermined program. This moves away from the idea that organisms can react and respond differently and in very complex fashion.

In their analysis of environmental-epigenetic research, David Witherington and Robert Lickliter (2017) describe two reductionistic explanatory patterns, firstly a strongly mechanistic language in which complex interactions are explained with the aid of statistical approaches and then presented using algorithms and formalisms, and secondly a molecularization of the nurture side of nature-nurture relations. What is meant here is that environmental phenomena are also classified and formalized using a specific scientific strategy to make them accessible according to the experimental procedures. On the one hand, environmental epigenetics is open to influences outside the organism and body and is specifically interested in the interaction of the various factors. Considering complex contexts such as living conditions, environmental epigenetic research produces an "embedded body" (Niewöhner, 2011) that points to all the aspects that cannot be explained by biological processes alone. Rather, bodies are now perceived as embedded in their environment and not as detachable from it. On the other hand, it can be observed that the attempt to operationalize environmental factors is accompanied by a "*physiologisation or molecularisation of body, biography and milieu*" (Niewöhner, 2011) and thus by a strong reduction of the considerable complexity of the total array of influencing variables.

2. Extracellular Vesicles, "Membrane Landscapes" and Non-Genetic Inheritance

Based on the above considerations, it is tempting to speculate about a rediscovery of Darwin's Pangenesis theory through the "back door", i.e., via so-called extracellular vesicles (EVs) and "membrane landscapes" (MLs). EVs are small vesicles (30 - 1000 nm) that are released into extracellular or environmental compartments by almost all eukaryotic donor cells in the course of protrusion of plasma membranes (PMs) (i.e., microparticles) or exocytosis along the endosomal and secretory pathways (i.e., exosomes), either constitutively or in response to environmental factors. EVs manage to trigger specific functional changes in appropriate acceptor cells either after fusion with their PMs (microparticles) or endocytic uptake and endosomal fusion (exosomes) (Valadi et al., 2007; Müller, 2012; Cocucci & Meldolesi, 2015; Yanez-Mo et al., 2015; Mathieu et al., 2019; Raposo & Stahl, 2019). The phospholipid bilayer membrane of the EVs with its integrated transmembrane as well as inserted glycolipid-anchored proteins may enclose soluble proteins and (small, circular, messenger) RNA and DNA, which together with the membrane originate from the donor cells. The use of EVs for diagnostics is currently being investigated for a variety of diseases ("liquid biopsies").

With the discovery of EVs harboring nucleic acids or free nucleic acids circulating in body fluids (Yakubov et al., 2002; Ziegler et al., 2002; Stroun & Anker, 2005) and prion proteins capable of self-replication (Wickner et al., 2004; Shorter & Lindquist, 2005), which either can be transferred from donor to acceptor cells or can be propagated in acceptor cells upon contact, the possibility of the existence of non-genetic matter of inheritance, operating in a similar fashion as "Gemmules", was again put up for discussion (Liu, 2008; Li, & Liu, 2010; Liu & Li, 2014; Liu & Chen, 2018; Liu et al., 2009).

MLs are configurations of membrane proteins in concert with (glyco)phospholipids of PMs of specific composition, inside-outside orientation and topographical configuration, which are transferred from donor to acceptor cells via EVs or micelle-like complexes (Müller & Müller, 2024). The latter consist of glycolipid-anchored proteins, (lyso)phospholipids and cholesterol, which on the basis of their amphiphilic character are capable of (self-)assembly in order to ensure compatibility with the aqueous environment. Micelle-like complexes are released constitutively or in response to specific (patho)physiological stimuli. Their use for diagnostics (biomarkers) is currently being intensively investigated (e.g., Müller et al., 2019).

If EVs and MLs were actually granted the "status" of a non-DNA matter of inheritance, even if they contain DNA (EVs) or are associated with DNA (MLs associated with mitochondria and chloroplasts) (only nuclear DNA is typically regarded as genetic material), this would have far-reaching implications, not only for the research practice of genetics, evolution and cell biology, but also for the theory, sociology and history of science. However, the current debate seems still to adhere tightly to the "DNA-centric" conception of inheritance with DNA acting as the one and only matter, whether being wrapped as chromosomes together with histones, encapsulated in vesicles or naked, whether being linear or circular, whether being of bacterial or human origin. So far, EVs have been mainly interpreted in terms of additional mechanisms for either signal transmission or the intercellular transfer of nucleic acids, which is not based on receptor binding and cell division or fusion, respectively, but relies on extracellular routes. And prions and their supposed inheritance have been classified as ("exotic") exceptions from the rule of the central dogma of molecular biology for a long period.

3. Self-Assembly Vs. Self-Organization

The replication of DNA is not "autonomous", although the structure of the double helix suggests operation of self-assembly due to base-pairing of the nucleotides of the two strands and the apparent need only for enzymic action of DNA polymerase. As a result, each daughter cell receives one strand of the DNA double helix from the mother cell which undergoes completion to a double strand by the complementary strand before transfer. So, in a certain sense, there is continuity of matter that is transferred from cell to cell, from organism to organism (even if it becomes more and more "diluted" with the generations). However, and often neglected, the DNA replication critically depends on a complex sophisticated apparatus involving many proteins (e.g., gyrase, topoisomerase), other nucleic acids (e.g., primers) and even membranes (to guarantee distribution to the daughter cells) which supports the semi-conservative mechanism of DNA replication, including its configuration as double helix and arrangement as chromosomes. Moreover, at a closer look at the initial stage, too, replication of DNA, apparently does not follow the rules of self-assembly, i.e., DNA is not generated "*de novo*", but rather by the incorporation of newly synthesized constituent components along an already existing "template". The resulting double strand consists of the "template", "original" or "positive" and the "print", "image" or "negative" derived thereof. The same principle holds true for the replication of PMs, organelles and MLs, albeit the machineries engaged differ fundamentally from each other. They all grow by the incorporation of newly synthesized constituent components in pre-existing assemblies and structures.

Pre-existing PMs, organelles, and MLs are indispensable prerequisites for providing shape to a new cell, separating the cell interior from the environment, organizing different reaction compartments, driving cellular metabolism, and expressing information encoded in the DNA. As a template, these (sub)cellular structures manage to direct the biogenesis of analogous functional assemblies in the daughter cells. Consequently, certain aspects of the cellular phenotype will be inherited, which may be interpreted as the information for the ontogenetic re-construction of a particular structural variant. "Structural templating" or cytoplasmic inheritance does not depend on *de novo* biosynthesis (Yaffe, 1999; Szathmáry, 2000; Moreira-Leite et al., 2001; Lockshon, 2002; Cavalier-Smith, 2004; Feldman et al., 2007; Beisson, 2008; Shirokawa & Shimada, 2016). This is the very reason why cells, irrespective of whether being of prokaryotic or eukaryotic origin, do not follow self-assembly and will not arise *de novo* upon construction of their genome with the aid of recombinant DNA technology, provided the transfer of a complete chemically synthesized genome or chromosome into pre-existing viable bacterial or yeast cells is not regarded as the *de novo* creation of new life, as has been postulated by some researcher engaged in synthetic biology and artificial life (Gibson et al., 2010; Venetz et al., 2019; Schindler et al., 2023).

By contrast, the "replication" or biosynthesis of individual cellular macromolecules, such as proteins, carbohydrates, or lipids, are generated *de novo*, i.e., they are built together from their constituent components (e.g., amino acids, monosaccharides, fatty acids) with the help of DNA as the "instruction" or information for their assembly into polymers, either directly by following the central dogma of molecular biology (proteins) or indirectly (lipids, carbohydrates) by means of enzymic synthesis. This means that the constituents of a particular entity of a protein, carbohydrate, or lipid to be replicated, are not passed on to a copy of this specific protein, carbohydrate, or lipid. So, there is no continuity of matter between the "old" and "new" entities of individual proteins, carbohydrates, and lipids. Temporal and spatial continuity could therefore be regarded as a criterion for the matter of inheritance, irrespective of whether being of DNA or non-DNA nature. No doubt, this criterion of temporal and spatial continuity is fulfilled by PMs, organelles and MLs.

The molecular mechanisms underlying the copying of, environmentally (in the broadest sense) induced, structural changes in the "membranome" and MLs as prerequisite for their transfer remain a matter of speculation. They may be facilitated by the well-known process of the so-called "self-templating" of proteins, in general, and of prions (i.e., proteinaceous infectious particles), in particular (see above). This is because those are proteins exhibiting the unusual property of expression of two or more stable, yet fully reversible conformations (i.e., so-called "prion alleles") which are associated with different functional states (Lancaster et al., 2010; Tikhodeyev et al., 2017). At least one of which, namely the "prion state", can multiply itself by "imposing" their spatial structure on homologous proteins with similar amino acid sequence. This may be regarded as "communicatable or hereditary memory of shape and order", like the phenomenon of paramutation (Tuite, 2015). Since the biological activity of proteins depends largely on their three-dimensional structure (Anfinsen & Haber, 1961), one and the same prion can exert different physiological effects. The phenotype associated with a prion conformation 1) behaves dominantly at crosses (conversion of proteins of the same type into the prion conformation), 2) is inherited via meiosis in a non-Mendelian manner (since there is no structural mutation) and 3) is cytoplasmically transmissible.

In addition, prions respond to milieu conditions and environmental factors, especially to cellular stress (in the broadest sense), by means of modifications of their conformation, which may also be transferred from donor to acceptor cells. Thereby, modified and well adapted phenotypes, such as the use of different nutrient sources, will prevail over less well-adapted conformers, which may be interpreted as a mode of selection (Halfmann & Lindquist, 2010; Harvey et al., 2018). The activation of prion proteins, i.e., the switching from the basal to the prion state, under certain environmental conditions is related to the fact that the "self-propagation" is linked to a molecular machinery maintaining the correct protein conformation in the form of chaperones (Tyedmers et al., 2008; Manjrekar & Shah, 2020). In a population, the diversity of hereditary phenotypes of genetically identical cells may be further enhanced by the fact that prion and non-prion conformations of different prion proteins can combine in a variety of ways (Newby & Lindquist, 2013). Prions are therefore "self-propagating" proteins that induce hereditary phenotypic changes and play a physiological role in the storage and transmission of environment-dependent structural information, in fungi (Liebman & Chernoff, 2012; Soto, 2012) and most likely also in most higher eukaryotes (Maglio et al., 2004; Wickner et al., 2004; Kussell & Leibler, 2005).

Prions and prion-like molecules can be interpreted as part of protein-based inheritance. Such "protein genes" (Uptain & Lindquist, 2002; Wickner, 2010; Newby & Lindquist, 2013) seem to operate as inducible sources of hereditary phenotypic variability with unaltered genotype and offer cells the opportunity to modify their phenotype in a variety of ways if such diversity is highly likely to be beneficial. Since they thereby affect both the non-random acquisition of rapid hereditary adaptations and new phylogenetic traits, some researchers have spoken of a "quasi-Lamarckian" mechanism of inheritance of acquired traits (Chernoff, 2001; Halfmann & Lindquist, 2010; Koonin, 2012). The same applies to an, apparently phylogenetically old, communication system between different bacteria, among them *Staphylococcus*, and the yeast *Saccharomyces cerevisiae* (Jarosz et al., 2014). Under certain environmental conditions, bacteria produce a signaling substance that induces a conformational change in a certain protein from the non-prion to the prion state in the fungus and thus changes the fungal metabolism in heritable fashion (i.e., over several hundred generations) in such a way that both the bacterial and the fungal cells benefit from it. It remains unclear so far to what extent such transorganismal prion-like, i.e., protein gene-induced mechanisms are operating between higher eukaryotes and to what extent similar DNA-independent copying processes also play a role in biological membranes and organelles, in general, and those exhibiting MLs, in particular.

Taken together, biological membranes and MLs do not obey the rules of *de novo* biosynthesis or self-assembly. They grow and replicate by the incorporation of the constituent components, proteins, and lipids, into pre-existing "mother" or "parental" PMs, organelles and MLs, which act as a type of template for "daughter" or "offspring" PMs, organelles, and MLs, like the one DNA strand during replication of the DNA double helix. As with DNA, there is continuity of the matter between PMs, organelles and MLs. Parts of the "mother" or "parental" organelles and MLs become part of the successor structures, which are passed on to daughter cells from one generation to the next. The successful transfer is critically dependent on their correct incorporation into the PMs, organelles and MLs to be replicated. These incorporation processes, highly specific for biological membranes and MLs, involve complex molecular machineries, which have been intensively investigated during the past five decades. In this sense, neither the replication of DNA nor that of PMs, organelles and MLs appears to be autonomous or even semi-autonomous, at least.

It is of crucial importance that MLs are susceptible to environmental factors and extracellular conditions, such as (oxidative) stress, mechanical pressure, UV, visible light, and manage to respond with specific changes in their topology, assembly state and three-dimensional configuration. Those changes may affect the overall shape and function of the cell and thus cause switching of its phenotype. And these environmentally induced changes can be replicated by the incorporation of newly synthesized protein components into the altered MLs. This results in adaptation of the specifically altered topology, assembly state and configuration by the newly replicated MLs which in the following will be termed "membrane environmental landscapes" (MELs), just to emphasize the tight interaction (i.e., intra-action, see below) of MLs and environmental factors. The replication and transfer of MELs and their environmentally induced topological changes, which may be regarded as "non-genetic mutations", could therefore represent a mechanism for the inheritance of acquired traits. Thus, MELs should be considered as dynamic and flexible rather than as stable and rigid structures, being capable to adopt a huge number of different configurations, assembly states, and topologies. Nevertheless, they will be capable of undergoing only certain defined and functionally relevant rather than any structural re-arrangements.

It is important to emphasize, that biological membranes, in general, and MLs, in particular, do not obey the rules of *de novo* or self-assembly. They grow and replicate by the incorporation of the constituent components, proteins, and lipids, into pre-existing "mother" or "parental" organelles and MLs, which act as a type of template for "daughter" or "offspring" organelles and MLs, like the one DNA strand during replication of the DNA double helix. As with DNA, there is continuity of the matter of organelles and MLs. Parts of the "mother" or "parental" organelles and MLs become part of the successor structures, which are passed on to daughter cells from one generation to the next. The successful transfer is critically dependent on their correct incorporation into the organelles and MLs to be replicated. These incorporation processes, highly specific for membranes and MLs, involve complex molecular machineries, which has been intensively investigated during the last five decades. Furthermore, it is of crucial importance that MLs are susceptible to environmental factors, such as (oxidative) stress, mechanical pressure, and manage to respond with specific changes in their topology and assembly state. Those changes may affect the function of the cell and thus cause switching of its phenotype. And these environmentally induced changes can be replicated by the incorporation of newly synthesized protein components into the altered MLs, which become transformed thereby into MELs.

Taken together, the replication and transfer of MELs and their environmentally induced topological changes, which may be regarded as "non-genetic mutations", could therefore represent a mechanism for the inheritance of acquired traits. Thus, MELs should be considered as dynamic and flexible structures and assemblies, being capable to adopt different configurations and topologies of defined rather than arbitrary structural re-arrangements. It may be tempting to speculate that MELs, which become distorted and thereby adapted to a specific environmental condition represents the materialization in the sense of acquisition of matter fitting best to this condition, i.e., the materialized characteristics expressed at the corresponding organism in response to the environment. In analogy, inherited acquired traits have sometimes been interpreted as the result of some (often ill-defined) materialization processes.

4. "Science and Technology Studies" (STS) and the "Poly-Matter Network" Conception of Biological Inheritance

With the observation of phenotype variation, the impact of environmental factors, such as nutrition and stress, in the differential regulation of gene expression has been widely accepted and resulted in intense efforts to resolve the underlying epigenetic mechanisms. Those, however, adhere to DNA (and associated proteins) as the only matter of inheritance and may explain the putative inheritance of environment-controlled quantitative differences in gene expression between generations, solely. In contrast, it is our argumentation that inheritance can only be adequately understood as the transfer of DNA in concert with non-DNA matter in a "poly-matter network" conception of biological inheritance. In greater detail, for its development, the DNA-/environment-centric conception has been supplemented with the various types of the (extracellular) transfer of

DOI: 10.4236/ahs.2024.132007

MELs from somatic donor to acceptor cells, involving either direct contact between them (trogocytosis) or the budding from donor cells and fusion with/uptake by acceptor cells of EVs or the release of micelle-like GPI-AP complexes from donor cells and subsequent insertion into acceptor cells. Thus, extracellular transfer of MELs is assumed to occur in addition to the intercellular transfer of MELs and of other non-DNA matter along with PMs and organelles between mother and daughter cells in the course of cell division. Transfer of DNA matter between somatic and germline cells within the same organism as well as parental gametes and the offspring zygote in course of cell division and fusion, respectively, and the operation of epigenetic mechanisms are fully acknowledged by the "poly-matter network" conception. However, at variance with a holistic view, the necessity to indicate the need of the continuous operation of environmental factors from generation to generation is considered to be dispensable.

For a better understanding of the "poly-matter network" conception, MELs should be considered as the product of "intra-action" between MLs of the PMs and the surrounding microenvironment, rather than as interaction, just to indicate that MLs and environmental factors do not exist as separate pre-formed entities, independent of each other, which eventually manage to interact with each other. Rather, MLs and environmental factors become generated as recognizable and stabilized distinct phenomena only in course of "agential separation" of the "intra-acting" MLs and environmental factors. Consequently, "intra-action" is a key concept of agential realism (Barad, 2003; Barad, 2014). In contrast to the usual "interaction", the term "intra-action" recognizes that distinct entities, agencies, events, practices, such as the different materials of inheritance, do not precede, but rather emerge from/through their intra-action, for instance as apparatus of production or observation of a phenomenon, such as the inheritable and environmental agents and agencies of (patho)physiological processes. "Distinct agents and agencies" are only distinct in a relational, not an absolute sense. That is, agents and agencies are only distinct in relation to their mutual entanglement. They do not exist as individual elements. As one consequence, intra-action constitutes a radical reshaping of the traditional understanding of causality.

The term and meaning of "intra-action" have first been introduced by the American physicist, feminist philosopher, and STS scholar Karen Barad (2003) during the development of a novel variant of "New Materialism" within the scope of a radical "material turn" (Hoppe & Lemke, 2021). This so-called "Agential Realism" challenges representalism as an adequate conception for the understanding of knowledge production. According to representalism, words, digits, images, or data generated by scientific apparatuses of observation objectively describe or represent pre-existing objects, i.e., both things and phenomena. Thus, objects and their representations have been claimed to be separate entities, independent of each other, which are linked only by a speech act attributing meaning (Hacking, 1983; Knorr Cetina, 1999). For Barad, the measured object *and* the apparatuses of observation, including the inscriptions emerging thereof, form a non-dualistic material entirety. In Barad's terminology apparatuses are not mere observing and inscribing instruments but rather practices of drawing of the material-discursive boundary, through which differential agential cuts between the objects and subjects lead to their generation, visibility and stabilization (Barad, 2003). In analogy, PMs, organelles, M(E)Ls, DNA *and* the corresponding apparatuses of observation and inscription, encompassing the researchers, such as scientists, technicians, the experimental procedures, such as incubation, pipetting, cell culture, blood transfusion, and the instruments used, such as centrifuges, gel electrophoresis chambers, biosensors, transwell co-cultures, culture plates, injection needles, draw the boundary between organisms and the environment, between the interior and exterior of organisms, between the cytoplasm and extracellular compartment, between matter and information of biological inheritance, between non-genetic and genetic matter. Some examples for the consequences of agential separation are given: isolated EVs or micelle-like complexes harboring MELs *vs.* acceptor cells during phenotypic (metabolic) switching in mammalian cells (Müller, 2018; Müller & Müller, 2023a, 2023b, 2023c), disintegrated donor cells or purified bacterial DNA *vs.* bacterial acceptor cells during transformation (Griffith, 1928; Avery et al., 1944), physical separation (by shearing forces) of donor *vs.* acceptor cells during bacterial conjugation (chromosome transfer) (Tatum & Lederberg, 1947; Stocker et al., 1953), some undefined matter in blood (e.g., "Gemmules", "Stirps") or other body fluids *vs.* mammalian acceptor organisms during infusion and parabiosis, isolated nuclei *vs.* amphibian acceptor organisms during nucleus transplanation, sperm *vs.* enucleated eggs during fertilization (for reviews, see Liu, 2008; Briggs & King, 1952; Gurdon, 1964).

In conclusion, various (sub)cellular materials, among them PMs, organelles, EVs and MELs, the surroundings and environment as well as the apparatuses of their observation and inscription, are actors in a "poly-matter network" conception of inheritance which are produced in the course of agential separation from one another. Concomitantly, that imprinted matter operates as the Bohr'sche and Barad'sche material-discursive apparatus (Bohr, 1985; Barad, 2014) of observation and inscription for the agential separation of the research objects, i.e., environment, cell, organism, body, and the research subjects, i.e., instruments, scientists, journal articles, as well as for their "intra-action". For this novel conception the traditional "DNA-/environment-centric" one had to supplemented with the various extracellular modes of the transfer of PMs, organelles, EVs and MELs, between somatic cells and between somatic and germ line cells. The underlying mechanisms involve either direct contact between donor and acceptor cells (trogocytosis) or the budding from donor cells and fusion with/uptake by acceptor cells of EVs or the release of micelle-like complexes from donor cells and insertion into acceptor cells. Thus, extracellular transfer of PMs, EVs and MELs is assumed to occur in addition to the intercellular transfer of organelles between somatic cells in course of cell division.

Certainly, the significant contributions of the transfer of DNA matter between somatic and germ line cells, and between parental gametes and offspring zygotes in course of cell division and fusion, respectively, as well as the operation of epigenetic mechanisms are fully acknowledged by the "poly-matter network" conception. In comparison, the "DNA-/epigenetics-centric" conception of inheritance (see above) provides a rather narrowed, i.e., "one-dimensional" explanation for the transgenerational effects of the environment on organisms and bodies which predominantly relies on the exogenous control of the expression of certain genes, i.e., of the amount of their RNA and protein products. At variance, the "poly-matter network" conception of inheritance bypasses this apparent narrowing and opens the multi-dimensional space of MELs for access by environmental factors encompassing their full diversity. Each of them, either alone or in concert, may induce (re-)configurations of the topography of MELs and organelles, leading to (re-)organized protuberances, valleys, blebs, invaginations etc., independent of whether being exposed at the surface (PMs) or hidden in the depth of the cytoplasm (at the nucleus, ER, Golgi, mitochondria). Thus, environmental factors produce inscriptions, spurs, marks in the MELs and organelles and thereby imprint their complexity/multi-dimensionality into that matter. It is of crucial importance to emphasize that the hypothesis introduced in this paper does and must not involve the simple replacement of the "DNA-/gene-centric" conception for the next "centric" one, in general, and a "prion protein- or a MEL-centric" one, in particular. However, the possibility or even danger of a putative "re-narrowing" is made unlikely for the following reasons: 1) The conceptions of both the actor-network theory and the agential realism favor the description of all human and non-human actors "intra-acting" within complex networks. 2) The non-separability or agential separability, only, of subjects and objects, interior and exterior, matter and discourse, nature and culture, genes and environment, nature and nurture, genetic and non-genetic matter of inheritance, respectively, which produces a phenomenon, such as inheritance, prevents overestimation of the impact of (a limited number of) specific actors and the exclusion of (the majority of) seemingly unspecified actors. 3) In general, a "centric" conception relies on two assumptions, "spatial depth" and "temporal stability". In case of the "DNA-/gene-centric" conception both of them are guaranteed by the concentration of the matter of inheritance in the cell nucleus, far away from the cellular periphery and protected from the extracellular environment through enclosure by a nuclear envelop and wrapping around numerous histone proteins as well as by the operation of efficient repair systems. Both the "spatial depth" and the "temporal stability" are seemingly (causally) linked to the apparent non-accessibility of DNA/genes towards "qualitative" alterations, i.e., nucleotide exchanges, driven by adaptations in response to environmental actors. In fact, DNA/genes are only prone to mutations, accidentally caused by radiation, chemicals, or errors in the course of replication or repair or to sequence changes as a result of (meiotic) recombination during sexual reproduction and bacterial chromosome transfer, respectively. Epigenetic modifications, such as DNA methylation or histone methylation or acetylation, which may be responsible for phenotypic plasticity in certain cases, do not contradict this view since they do not affect the nucleotide sequence of a given DNA/gene, but rather only "quantitatively" modulate its expression level (for a review, see Dupont et al., 2012; Feil & Fraga, 2012; Vukic et al., 2019; Bhattarai et al., 2021). No doubt, DNA/genes and their copying and transfer mechanisms are not compatible with "re-writing" of the "book of life" by either non-human or human actors, e.g., nutrition, breeders, and irrespectively of whether intention being involved or not, unless certain versions of "creationism" have succeeded in (re-)gaining credibility.

At contrast, "spatial depth" as well as "temporal stability" cannot be attributed to the different types of MELs. They are all directly exposed to extracellular compartments and may be directly affected by environmental actors, such as mechanical pressure or oxidative stress. These could lead to considerable alterations in their structure and topology, such as distortions, compressions, prolongations, as a consequence of adaptive processes, which will persist and be replicated even after termination of the environmental cues inducing them. Apparently, the missing "spatial depth" and "temporal stability" of the different types of MELs have not favored their interpretation as biological matter of inheritance by scientists as well as laymen so far and thereby prevented the development of a "MEL-centric" conception. Rather, instead of replacing one conception with the next "centric" one, a "poly-matter network" conception of biological inheritance will be proposed (Müller, 2024). It relies on a multitude of actors encompassing but not restricted to DNA, genes, proteins, lipids, PMs, organelles, MELs, environmental factors, donor/parental and acceptor/offspring organisms, researchers, the laboratory, and experimental set-ups, including journal articles and reviews, which in concert generate the material-discursive apparatuses of production and observation of the phenomenon of inheritance. According to this conception, the subject and object of observation as well as the donor/parental and acceptor/offspring organisms should be interpreted as only agentially separable rather than as distinct entities. The consideration of the meaning and agency of agential cuts and the simultaneous shift from the Cartesian to Bohr's and Barad's view of representation may lead to advantages in the future investigation of common complex diseases, in general, and metabolic diseases/syndrome, in particular, beyond the scope of typical, and no doubt very important, epigenetic studies for environment-, nutrition- and life style-driven diseases (for a review, see Mahmoud, 2022; Zoghbi & Beaudet, 2016; Tabatabaiefar et al., 2019). The adequate inclusion of the transfer of non-DNA matter is still a desideratum of future genetic research, which may pave the way for the experimental elucidation not only of how DNA and non-DNA matter act in concert to enable the inheritance of innate, but also whether they interact to foster inheritance of acquired of acquired biological traits. Moreover, the "poly-matter network" conception may open new perspectives for an understanding of the pathogenesis of "common complex" diseases, such as diabetes mellitus, with their non-Mendelian type of inheritance.

5. "Diffractive Reading" or "Entanglements" of Biological Inheritance

Agential realism is relevant for a better understanding of the inter- or rather intra-action of genes and environment in the pathogenesis of common complex diseases: This relevance relies on the methodology of Barad, in particular her "diffractive reading". Characteristic of agential realism is that Barad acknowledges differences, classifications, dichotomies, such as between genetic and non-genetic matter of inheritance or between genes and environment but does not take them for granted and set as unambiguous, and instead tries to make their emergence comprehensible, their origin understandable. This is achieved with the help of the concepts of agential apparatuses of the production and observation of phenomena, intra-actions, agential cuts and cutting things apart together or together apart. The differentiation between genetic and non-genetic matter necessitates an agential cut by apparatuses of production and observations of inheritance phenomena which are constituted by a multitude of both human and non-human actors, encompassing but not being restricted to PMs, devices of experimentation, measurement and documentation, such as centrifuge, mass spectrometer, gel electrophoresis chamber, surface acoustic waves biosensor, computers, scientific journals as well as researchers handling with these instruments of inscription and writing the papers and experts or laymen interested in the produced inscriptions who read the papers and draw conclusions. Certainly, it will never be possible to recognize and include all the (human and non-human) actors involved in the production and observation of a specific phenomenon, which may presumably or possibly be relevant for "diffractive reading" as a method for the description and understanding of the emergence of classifications, differences, and dichotomies. But "diffractive reading" should not be misunderstood as an argument for the consideration of seemingly "naturally" emerging actors, exclusively, and concomitantly exclusion of actors apparently failing to contribute to the phenomenon.

Barad describes her approach as "diffractive reading", an interweaving of scientific phenomena, experimental practices, feminist theories, discourse analyses, perspectives on the philosophy and sociology of sciences and media, and much more. This specific reading through each other and manifold interweaving of different and diverse, and often contradictory and unexpected, disciplines, discourses and theories describes the "diffractive" method as being tied in with the physical phenomenon of diffraction. Donna Haraway was among the first who proposes a "diffractive" methodology as a critical practice, to make differences in the world and to understand them as well as their emergence and agency (Haraway, 2017).

Karen Barad points out that many epistemologies and methodologies use optical metaphors and that the idea of representationalism is oriented towards the idea of reflection as a (critical) scientific practice. With this, Barad explicitly picks up on Donna Haraway (1997), who is concerned with drawing attention to the differences that arise in and through science production (Barad, 2011: pp. 443-454). Reflection describes that something is reflected, distracted, mirrored, and it is of interest to stay as close as possible to the "original", the "truth". Importantly, both Haraway and Barad distance themselves from this perspective and do not assume that critical reflection as neutral observer from a distance is possible as a prerequisite for good scientific practice. They propose a "diffractive" methodology as a critical practice, as it is a matter of understanding which differences matter, how they affect matter, and what becomes visible beyond differences (Barad, 2007: p. 90). With diffraction it becomes clear that the possibility of independent representation of phenomena is not given *per se*, since they are intra-actively constituted and entangled phenomena, and the practices of knowledge production are situated around complex and living configurations.

In the radical questioning of defined, stable and separable entities, such as genes, proteins, lipids, membranes, MELs, environmental factors, and the differences between them, Barad shifts the focus to boundaries and entanglements (Barad, 2007: p. 73). To do this, it needs apparatuses of diffraction. At the same time, she is aware of the difficulty of developing such an apparatus and responsibly investigating entanglements that change again with each intra-action (Barad, 2007: p. 74). Barad explicitly speaks of apparatuses that need to be developed for every (natural) scientific phenomenon. However, this does not mean being able to design or program an apparatus once that then fulfills its task. Apparatuses in Barad's sense is much more, namely, the "*material conditions of possibility and impossibility of mattering*" (Barad, 2007: p. 148). Specifically, Barad states that she reads different theories, discourses, and disciplines through each other, making her vulnerable for attacks by the individual actors.

When Karen Barad discusses her understanding of matter, discourse, and other aspects, she explicitly draws on works by Niels Bohr, Michel Foucault, and Judith Butler (Barad, 2007: p. 135). Certainly, one could argue that every scientist is always influenced by numerous other people, theories, discourses, etc., in his/her (experimental) work, thinking, discussing, writing, and that these merge with each other in their own projects, overlaid by numerous influences feeding into them. Barad, on the other hand, does it quite explicitly, marking who she is including what from, and broadening her own view across disciplines. Thus, their "diffractive" reading is to be understood as a stimulus not only to work with familiar terms and understandings, but also to draw on different disciplines, perspectives, and concepts, and to open one's own view and stimulate new ways of thinking through the combination and superimposition, as in the case of light waves. Barad combines works from authors who don't usually meet. For an approach that is aimed to radically question and to shift all differences, but that does not deny them, it is necessary to soften disciplinary boundaries and to include concepts from the social and natural sciences. This is another reason why Barad could be helpful for the future study of the phenomenon of biological inheritance, with its underlying intra-action of genes, proteins, lipids, membranes, organelles, and MELs, where social science and theory, feminist theory, historical sciences and the philosophy and sociology of science encounter a common field. The formidable challenge herein is not to put any of the theories, discourses and disciplines above the other.

Karen Barad tests "diffractive reading" by assembling the text from different sections, called scenes, and often first specifying what is being diffracted in each case. In doing so, she brings together different discoveries, times, "theatre scenes or places" and aims to convey a feeling for intra-activity, agential separability, cutting thing together apart and quantum entanglement through this format (Barad, 2010: p. 245). A perusal of agential realism and the phenomenon of biological inheritance will be fruitful and reveal new human and non-human actors involved in the analysis of novel functions of DNA and genes, others than those produced by the canonical categories of informational analysis (Dickins, 2023) and (multi-)causal specificity (Ferreira Ruiz, 2021; Vecchi & Santos, 2023) as well as experimental practices, such as knock-out and transgenic (animal) models. With "diffractive" reading, it will be possible to search for differences of the matter of inheritance and their resolutions in a less one-sided way and to look more openly beyond the current state-of-the-art in studies in genetics and molecular biology, and what else is happening in both related and distant areas. The reader should keep in mind that there are multiple interpretations of quantum physics. So why should there be one and the only interpretation of biological inheritance?

6. Causal and Explanatory Approval of Conceptions of Inheritance

As delineated above, DNA and environmental factors are not sufficient for the development of reliably recurring inherited traits and phenotypes, apparently making the "DNA-/environment-centric" conception of inheritance obsolete. Nevertheless, this view is currently not being shared by the scientific community of geneticists and molecular biologists. For a better understanding of the reasons for the neglection of a "poly-matter network" of inheritance, first the idea of causal and explanatory approval, as initially introduced by Wheeler and Clark (1999), will be presented.

Accordingly, causal approval means the identification of a new factor that is causally responsible for the occurrence of a particular phenomenon. Explanatory approval is understood to mean when, for a certain factor that was previously not assumed to be necessary for the explanation of a particular phenomenon, it now turned out to be of critical importance for the understanding of this phenomenon. Or to put it another way, explanatory approval always comes in mo-tion when it has become obvious that a certain factor, which has not previously been part of a sufficient explanation for a particular phenomenon, must now be included in such an explanation. Thus the fact that a factor is causally necessary does not necessarily mean that it is also considered to be explanatorily necessary. Causal approval does not automatically lead to explanatory approval. But at least in cases where it can be assumed that the newly discovered causal factor plays a critical role, it is very likely that the causal approval of this factor will lead to its inclusion in any sufficient explanation for the phenomenon for which this factor is causally required to occur in reliable and recurring fashion. In such cases, causal approval entails explanatory approval.

If, for instance, one wants to explain why in a certain restaurant a certain favorite menu has the same excellent taste every Sunday lunchtime week after week, it should be noted in this explanation that the recipe and the cooking equipment used (e.g. knives, wooden spoons, oven) are always the same, that the ingredients used (e.g. meat, potatoes, vegetables, spices) are always of the same quality (e.g. delivered by the same farm and other producers) and that the menu is always cooked week after week by the same team of cooks with the same very good training and in the same good mood. And if it is true that all these factors are required for the consistent taste of the menu in consistent quality, then it would be necessary to specify how the consistency of quality over weeks is achieved and guaranteed (i.e., business strategy for quality control and assurance).

This simple example can be applied to reliably recurring inherited phenotypic traits: Assuming that two DNA actors G1 and G2 and two environmental actors E1 and E2 are necessary for the explanation of a reliably recurring phenotype P, this explanation would also have to indicate how it is achieved that G1, G2, E1 and E2 also occur reliably again and again. However, this also means that the DNA and its replication and transfer are not sufficient for the reliable occurrence (i.e., inheritance) of P. DNA replication and transfer may be sufficient to explain the reliable recurrence of the actors G1 and G2, but they do not explain the reliable occurrence of the actors E1 and E2. It follows that actors and actions that are not identical with DNA and its replication and transfer and that adequately explain the reliable occurrence of E1 and E2 must be included in a sufficient explanation for the reliable return of P, as may be exemplified by the adequate explanation for the inheritance of mammalian legs and other features.

Why do the shape and structure of legs of a human descendant reliably resemble the shape and structure of the legs of the parents? Such an explanation will have to mention not only the reliable return of DNA involved in the development of human legs, but also the fact that humans are subject to virtually the same gravity forces from one generation to the next (Hammond et al., 2000; Cogoli, 2002). And this means that adequate explanations of the reliable recurrence (i.e., inheritance) of legs of a particular shape and structure in human lineages must include not only the replication and transfer of DNA, but also those actors and actions that explain why human beings experience gravity forces of the same strength over generations. Similarly, if the reliable occurrence of "normal" skin, teeth, vessels and joints in human lineages is to be adequately explained, it is necessary to name not only the reliable recurrence of the DNA involved in the development and maintenance of those features and the actions of their replication and transfer, but also the fact that ascorbate at a sufficient concentration has to be reliably available to and consumed by people from generation to generation, as well as the actors and actions that reliably guarantee this, such as a reliable chain of supply of fresh fruits. Such examples could be continued indefinitely (Griffith & Gray, 2001; Szathmáry, 2000; Sterelny, 2001).

Moreover, in addition to environmental and genetic actors, those of non-DNA matter must be considered, too: Assuming that two genetic actors, G1 and G2, and two actors of non-DNA matter, M1 and M2 (e.g., MEL1 and MEL2), are necessary for the explanation of a reliably recurring phenotype P, this explanation would also have to indicate how it is achieved that G1, G2, MEL1 and MEL2 also occur reliably again and again. Again, this does mean that the actor DNA and its actions of replication and transfer are not sufficient for the inheritance of P. DNA replication and transfer may be sufficient to explain the reliable recurrence of G1 and G2, but they do not explain the reliable recurrence of MEL1 and MEL2. It follows that actors and actions that are not identical with DNA and its replication and transfer and that adequately explain the reliable recurrence of MEL1 and MEL2, their intercellular transfer through EVs and micelle-like complexes must be included in a sufficient explanation for the reliable return of P. Or in the case of ER or mitochondria as non-DNA material actors, the secretory pathway and post-translational biogenesis, respectively, represent adequate explanations for the reliable recurrence of P.

In conclusion, the reliable recurrence of a phenotypic trait cannot be explained solely by DNA and its replication and transfer, i.e., by actions that explain the reliable recurrence of genetic traits. In addition, reference must also be made to the actions that explain the reliable occurrence of non-DNA matter in sufficient explanations of the development of a phenotype. The inheritance of phenotypes is thus explained by the replication and transfer of both DNA (and its modifications) and non-DNA matter, e.g., (prion and intrinsically disordered) proteins, PMs, organelles, MELs, and environmental actors, e.g., gravity, food ingredients, UV-light. Importantly, the non-DNA environmental and material actors may "intra-act", as becomes manifest in MELs. Thus, contentment with explanatory rather than with causal sufficiency or neglection of the latter in favor of the former by the scientific community of geneticists and molecular biologists inevitably leads to preference of "DNA-/epigenetics-/environment-centric" *vs.* "poly-matter network" conceptions of inheritance.

In general, the decision about inclusion or exclusion of actors and actions which are causally involved in the production of a phenomenon into or from, respectively, the explanatory foreground or background, i.e., their binary differentiation into those which are both necessary and sufficient for an explanation of the phenomenon (albeit they are not sufficient for its emergence) and those which are not necessary for an explanation (albeit they are necessary for its emergence) is made by the apparatuses of observation and inscription, which emerge from complex networks of human and non-human actors in the course of material-discursive practices. The description of the human and non-human actors and their multiple "intra-actions", which produce the differentiation between explanatory and causal sufficiency for the various conceptions of inheritance may have impact on the future development of genetics.

In addition to pragmatic reasons, there are additional strong arguments in favor of preferring the "poly-matter network" *vs.* the "holistic" conception. This can be understood best by using again the distinction between explanatory and causal sufficiency. Of course, it is true that very many, possibly almost each, part(s) of a life cycle (i.e., of the predecessor organism) is (are) causally required to produce the following life cycle (i.e., of the progeny organism), which displays very similar features. However, not each of these parts needs to be explicitly mentioned in a sufficient explanation for the reliable recurrence of that biological trait. To explain the occurrence of DNA from one generation to the next, the reference to their actions of replication and transfer, at least in most cases, is sufficient in terms of explanation and there is no reason to mention other parts of the life cycle of the predecessor organism. To explain, for example, the recurring exposure to gravity force on earth, it is only necessary to mention the stability of its size (which is ultimately determined by the mass of the earth). Details of the life cycle do not need to be mentioned at all in this example, eventually except of the size of the organism and the notion of an impact of gravity on the development of that organism. This seems to be predominantly the case in (larger) vertebrates and less so in non-vertebrates or, the more so, unicellular organisms, although some mechanisms have been described by which gravity fields can cause certain effects on small organisms (Cogoli, 2002; Hammond et al., 2000). Thus, a "poly-matter network" conception of inheritance of biological traits can be considered as pragmatic and explanatorily sufficient and should be preferred to a "holistic" one.

7. Conclusions

Criticism of the "DNA-(environment-/epigenetics-) centric" conception(s) of heredity has been raised by many scientists over the decades to variable degrees (Paterson & Gray, 1996; Sterelny, 2000; Fox Keller, 1995; Maynard Smith, 2000; Griffith, 2001; Nelkin, 2001; Sapp, 1987, 2003; Avital & Jablonka, 2001; Odling-Smee et al., 2003; Venville et al., 2006; Walsh, 2020). However, in most cases the argumentation was different from the one presented here. Only two major differences are presented here:

1) System theorists within developmental biology are often of the opinion that a critique of the concept of "genetic information" is *per se* of fundamental im-

portance for a rejection of the "DNA-(environment-/epigenetics-) centric" conception(s) of inheritance, or even that it is implied by it (Immelmann, 1975; Gray, 1992; Lacey, 1998; Maynard Smith, 2000; Sterelny, 2000; Griffiths, 2001; Nelkin, 2001; Gottlieb, 2003; Odling-Smee et al., 2003). Albeit the concept of "genetic information", as already indicated, is in fact of only, limited, theoretical value and does not contribute much to the practice of experimental research, the questioning of the "DNA-(environment-/epigenetics-) centric" conception(s) of inheritance by the "poly-matter network" does not rely on overemphasizing the problems with the term "information".

2) System theorists within developmental biology have often claimed that the "DNA-(environment-/epigenetics-) centric" conception(s) of inheritance should be abandoned in favor of a "holistic" theory of inheritance (Lewontin, 1993; Aufderheide, 2002; Hurst, 2002; Margulis & Sagan, 2002). According to this, the complete life cycle of a progenitor organism is indispensably involved in the regeneration of all those resources and in the reconstruction of all those interactions that are required for the beginning of a new life cycle of a progeny organism with the same characteristics.

With the identification of the transforming principle in bacteria, DNA has been acknowledged as the carrier matter for genetic information, in terms of a materialized "book of life", which apparently is both necessary and sufficient for the synthesis not only of proteins, but rather of all cellular building blocks and, in consequence, for the development of the complete organism. With the observation of phenotypic plasticity, i.e., the failure to explain the variation in phenotype between individual organisms exclusively by mutations and polymorphisms in their genome, the impact of environmental actors, such as nutrition and stress, in the differential regulation of gene expression has been widely accepted and resulted in intense efforts to resolve the underlying epigenetic mechanisms. Most critically, the exclusion of the existence of matter of inheritance different from DNA led to the ultimate refutation of the old and heavily disputed concept of inheritance of acquired features (since otherwise "the book of life" would necessitate its rewriting by environmental, human or non-human, actors. In this study, I intended to shift the "DNA- and information-centric" conception of biological inheritance with its exclusion of any non-DNA matter to a "poly-matter network" conception which, in addition to DNA, considers the action of other cellular constituents, in particular PMs in concert with environmental factors and their topological diversification as MELs. MELs, which replicate in acceptor cells by self-organization and self-templating (rather than self-assembly), are transferred from donor to acceptor cells by various, vesicular and non-vesicular, mechanisms and cause novel features in the acceptor cells. In the future, acceptance of a "poly-matter network" conception of biological inheritance may pave the way for the experimental elucidation as to whether DNA and non-DNA matter act in concert to enable the inheritance of not only innate but also of acquired traits.

The time is now more than ripe to re-vitalize this dispute and to broaden the "DNA-centric" to a "poly-matter network" conception of inheritance. The inheritance of biological traits can only be adequately understood as the transfer of DNA and non-DNA matter and appropriate environmental actors during "intra-actions" that produce both substance(s) and shape(s) for the development of cells, organisms, bodies, and the environment. The copying of DNA, its transfer and its transformation into proteins may be sufficient to explain the phenomenon of biological inheritance of traits in the foreground, but these actors and actions are not sufficient to understand it in depth, and at least in part causally. While over the past five decades much attention has been paid to the environmental actors, the adequate inclusion of the transfer of non-DNA matter is still a desideratum of future genetic as well as cell and molecular biology research.

The meanwhile canonical "DNA-/epigenetics-/environment-centric" conception of biological inheritance, according to which the vertical transfer of DNA in concert with specific environmental actors guarantees the reliable recurrence of phenotypic traits, should be extended to a "poly-matter network" conception by the inclusion of both vertical and horizontal transfer of non-DNA matter. It is of particular importance that the latter conception is compatible with the possibility of environmental actors operating in a "targeted" fashion, i.e., adaptively, on the non-DNA materials in vertical as well as horizontal lineages rather than only vertically and randomly via the induction of mutations in the genes of primordial cells or gametes as claimed by the "DNA-/environment-centric" conception. This opens new perspectives for an understanding of the pathogenesis of those diseases that have so far eluded adequate explanation by, one or many, gene(s) and/or, one or many, environmental actor(s), i.e., for so-called "common complex" or "civilization" diseases. Moreover, the "poly-matter network" conception of biological inheritance could lead to a revival of a state-of-the-art material-discursive practice on the inheritance of acquired biological traits, with all its potential opportunities and challenges for the individual (e.g., family planning, education), societal (e.g., school system, health care system) and political (e.g., racism, transhumanism) thinking and acting.

In particular, the consideration of a multitude of distinct actors, belonging to very different categories but contributing all to the phenomenon of donation and acceptance in the course of biological inheritance, will overcome the dualistic thinking and classification in terms of DNA *vs.* environment, information without meaning (i.e., DNA) *vs.* information with meaning (i.e., MELs), form (i.e., MELs) *vs.* substance (i.e., phospholipids, GPI-APs, cytoskeletal components), information for the biosynthesis of proteins (i.e., linear genetic code) *vs.* information for the biogenesis of subcellular structures (i.e., three-dimensional topology and orientation), interior *vs.* exterior, genetic *vs.* epigenetic mechanisms, nature *vs.* nurture, nature *vs.* culture, innate *vs.* acquired features, nuclear *vs.* protoplasmic inheritance. It is important to mention that the "poly-matter conception" should not be understood as one of synthesis. Rather than synthesizing different perspectives, so-called diffraction experiments and the method of diffractive reading through apparently dualistic views leading to different differences have to be performed, thereby trying to get a feel for how differences are produced and how they matter (Müller & Müller, 2024). The very notion of difference, that is the fact that differences are made, not found, and that dichotomies derive from particular cuts will lead to deconstruction of the presumed given-ness of dichotomies, which is a fixture of our Cartesian inheritance. Future investigations will reveal whether there is any correspondence or relationship between the dichotomies of DNA vs. non-DNA structures and those of free or liberal vs. social or socialistic economic systems, anti-authoritarian vs. "mandarine"-like educational and school systems, democratic vs. autocratic political systems, self-responsible vs. paternalistic health care systems. No doubt, the knowledge about the production of those dichotomies in relationship to those of mechanism vs. vitalism, reductionism vs. holism, disciplinary research vs. "Gestalt" theory, individual components vs. systems theory, self-assembly vs. self-organization, transmission genetics vs. developmental biology, nuclear monopoly vs. structural complexity will shed new light on the actors involved, the practices used, and the aims intended.

Conflicts of Interest

The author declares that he has no conflict of interest.

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