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THE RISE AND FALL OF THE CAUSE IN ÆTIOLOGICAL MODELS: INFLUENCES, GENE, ENVIRONMENT

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SUMMARY

Understanding the transformations in the history of ætiological models means understanding also the changing of the notion of cause. From a historical-epistemological standpoint recent ætiological models broke the monotheistic concept of cause and blurred it in a pluralist pantheon of interacting risk factors, the determinants of health and disease (genetics, behavioral, environmental and social). However, plural ætiology centered on the role of the interaction is not novel in medical history, especially when dealing with hereditary diseases. Since antiquity hereditary matters comprised a variety of causes, or influences (astrological, constitutional, congenital and environmental in general) at the crossroad of the nature-nurture interaction. As result of the FIRB project "For a Lexicon of genetics and its degenerations from Hippocrates to ICD-10" emphasizing the dialogue between ancient and modern medical concepts, I discuss here the main shifts of the notion of cause addressing generation and hereditary theories by means of a two step-analysis. In the first part, I will outline the notions of influence and interaction highlighting the main theoretical turning points about medical causality. In the second part, I will review the nature-nurture distinction in the field of heredity underlining the dichotomy between genetic and environmental factors throughout times. As a matter of fact, heredity reveals a most suitable tool for explaining the development of ætiological paradigms in the light of the nature-nurture debate.

Key words: Cause - Ætiology - Heredity - Interaction - Genetics - Epidemiology

Multiple causes and eugenic control: from the Bible to medicine and philosophy

Past, and present, ætiological reflections entail both empiric and theoretical issues. Despite Hippocratic western medicine developed as a natural *techné* distancing itself from philosophy its theoretical legacy is particularly emphasized when confronting with causality. On the other hand, in the humoralist paradigm with regards to ætiological explanations there was coalescence between "nature" and "culture" which has been pervasive and longlasting. A turning point can be singled out in the debate about hereditary diseases focused on a variety of causes (astrological, constitutional, congenital and environmental in general). The unfolding of the nature-nurture distinction in the early XIX century provided a different experimental and theoretical framework for hereditary issues. Along these lines, from the viewpoint of the history of ætiological ideas an unequivocal shift occurred: a plural system of causes was replaced by a conception of specific causality.

As result of the FIRB project "For a Lexicon of genetics and its degenerations from Hippocrates to ICD-10" this chapter aims to show how the ætiological debate interwove with and was influenced by the relation between nature and nurture within the development of hereditary theories. According to the focus of the FIRB project, which aimed at highlighting a parallelism between the ancient and the modern medical thought, I will discuss my specific and confined standpoint emphasizing conceptual bridges but without pretension to exhaustive coverage from a historical point of view.

The issues of heredity and hereditary causes of diseases are indeed interdisciplinary. Since ancient times they included medical, biological, philosophical and theological thought as well as beliefs and practical knowledge. First of all, it may be worth recalling that "heredity" is a metaphor. It comes from the corpus of law (from Latin,

hereditas) designating the way property passed on from father to son[1]. As often happens in scientific theory building[2], the metaphor of heredity was later transferred into the biological field acquiring its scientific meaning. Thus, the roots of the scientific concept of heredity are plunged into the past. Generation, transmission of characters, and resemblance between forebears and descendants are issues that have always awaken interest and curiosity. For instance, the simple observation of hereditary transmission of physical or behavioral characters through generations was exploited by breeders who selected the most robust and powerful lineages of horses and of other domestic livestock. An ancestral example can be found in the *Bible*. In the episode "Jacob's flock" [*Genesis*, 30, 25-43], Jacob by means of basic eugenic techniques within six years was capable to build a huge selected flock of sheep with two specific traits: variegated hair and vigorous constitution [*Genesis*, 31, 41].

Artificial selection challenged also the eugenic control of human traits, which would turn out to be an abiding issue for human heredity; to the point that it can be pointed out that the history of human heredity is a eugenic history[3]. An example can be highlighted in Plato's third book of *Republic* where Socrates describes the "myth of the metals" emphasizing a conception which links four citizens' lineages to their social class. The gold lineage (G) is the most adapt for governing, the silver lineage (S) is devoted to auxiliary jobs, the bronze lineage (B) is consecrated to workers, and the iron lineage (I) to peasants. With a declared anachronistic metaphor I dub this the "metallic code", an elementary "genetic" code (G-S-B-I) that is transmitted through generations. This inflexible paradigm that let every generation stuck to its metal and correspondent job, however, was subject to natural variance. Individual variability, consequence of the natural melting between metals, jeopardizes the stability of the law pairing the metal and the moral virtue, and thus the merited job. Consequently, the eugenic control of hereditary traits passed onto politic jurisdiction.

Along these lines, Sparta eugenic legislation imposed that children considered unfit for maintaining the robustness of the Spartan population were eliminated through infanticide (negative eugenic).
The Italian historian of medicine Voltaggio underlined that ancient philosophy and medicine were so entangled that if the Hippocratic text *Regimen* is implicitly philosophical and political the Platonic *Republic* on the contrary is implicitly medical[4]. This philosophical/medical/political perspective concerning the causes of heredity emphasized two strictly correlated elements. The first was the variability of *physis*, which is associated to individual's nature and individual variability. The second is the Hippocratic model of *poliarcheia* or individual complexity, by which individual's complexity mirrors the complexity of the cosmos. In this framework, heredity epitomizes the most intimate relation between individual's life and individual's history both bound up with the general course of natural processes.
From the ætiological standpoint, the intertwining of the concepts of "predisposition" and "familiarity" of diseases, along with the general individual's "constitution", "temperament" and "diathesis" characterised individual variability and the transmission of traits from parents to offspring[5]. In the humoralist paradigm with regards to hereditary matters causality is one among many and this pluralist ætiological model is entirely permeated by the entanglement of natural and cultural causes, or in other terms, the distinction between natural and cultural causes did not make sense. Within this background the development of the notion of "heredity" becomes a champion for observing the slow disentanglement of the natural cause of heredity developing from the original coalescence between nature and nurture.

Hereditary influences: from generation to reproduction[6]

Medieval has been considered a repository of questions that we do not ask anymore[7]. Anyhow, recently the literature is highlighting interesting discoveries from this epoch concerning the development of the

notion of hereditary disease[8]. Coalescence or disciplinary fluidity between religion, philosophy, and medicine informed concepts and theories, the physical level overlapped onto the metaphysical and the theological one, which represented the outer framework. Therefore, also in the debate about heredity, metaphysical questions, such as the creative power of generation, the production of novelty and spontaneous generation, were central and will be long-lasting issues[9]. However, the exchange between natural and metaphysical issues was not one-way. For instance, the literature has recently underlined that the idea of latency of disease, such as in the case of leprosy, would derive from a theological notion[10]. "Spiritual latency" may have suggested to physicians to reflect upon the issue of a cause of disease able to manifest its onset at distance, and with delay. This and other evidences led the literature proposing that in medieval physicians' disputes the issue of heredity was not alien to naturalistic and material interpretations[11].

In my brief excursus I shall now confine myself to two examples of hereditary issues in modern times showing the level of compliance in the generation process between the notion of *causality* and that of *influence*[12].

Firstly, Tasso in an episode of the *Jerusalem delivered* dubbed "Clorinda's birth" tells how the daughter of the royals of Ethiopia, both of colored skin, was born snow-white. The cause of this paradox was the strong impression of the portrait of "Saint George and Birutawit" (the girl from Beirut, with white skin) that "whitely imprinted" the queen's imaginative faculty, and accordingly allowing she could generate a white-skin daughter[13]. Currently this conception still impinges on the idea of birthmarks on child's skin which mirror mothers' desire of something, like chocolate or strawberry.

A second example is the *Geneanthropeia*, published in 1642 by the Italian physiologist and gynecologist Giovanni Benedetto Sinibaldi (1594-1658), which uniquely portraits human and animal generation, just before revolutionary discoveries about ovism and spermism

took place, as in Stensen's, De Graaf's, and van Leeuwenhoek's studies. For instance Sinibaldi describes how surrounding brooding peacocks with white towels allows them generating white creatures. He reports also that adultery couples feeling guilty during sexual intercourse would generate corrupt children, while too savvy men who think even during sex prevent vital spirits passing into their semen generating foolish kids. In this framework, imagination, environment and behaviors are all causes or determinants of generation and hereditary transmission by means of impressions[14]. Matter is extremely supple and permeable, and multiple *external causes* are like to influence the *internal* development (constitution) of the embryo.
Not surprisingly also the embryological debate was informed by metaphysical elements and by the coalescence between natural-cultural causes.
Since Aristotle's dualistic definition of preformationism and epigenesis, the debate on formal/material and efficient/teleological cause involved in the generation process has never ceased[15]. Together with the explanation of the "internal movement" in the incipient organism, modern biology faced one main metaphysical issue: the *genesis of form* in the embryo opposing epigeneticists' and preformists' explanations[16]. Here, for the sake of the argument, it should be synthetized that this debate focused on the development of form as the cause of development rather than on the cause of hereditary transmission. At the same time, mathematicians and philosophers were debating about ontological definitions of objects, such as magnitude, or quantity. From a theoretical standpoint, hereditary theories lacked similar definitions: a specific ontological "magnitude" within which hereditary transmission from parents to offspring was explainable by means of a specific, *quantitative* rather than *qualitative* entity. As discussed below, this passage would be acquired only later thanks to the ontologisation of the metaphor of heredity. Therefore, according to our contemporary western gaze in ancient and modern times the

notion of *influence* is more adapt for defining the porous causal relationship between individual and environment. The notion of influence rather than that of cause better tolerates also qualitative aspects within ætiological and hereditary explanations.

The growing hiatus between the general notion of heredity, which embodied creeds, ideology, metaphysical and theological issues, and the latent naturalistic one, slowly made the scientific definition of heredity emerging. For this passage a changing in the notion of cause was necessary, albeit not sufficient: for distinguishing all the multifactorial qualitative influences in the generation process the distinction between natural and cultural factors became decisive.

As Müller-Wille and Rheinberger underlined[17] a key turning point occurred in the theoretical passage from "generation" to "reproduction" despite not in univocal, definite and definitive way[18]. The mechanic of the embryo developed along with the mechanist gaze spread through XVIII and XIX century from physics and mathematics to physiology and medicine[19]. In a long multifaceted process, organisms' reproduction, opposed to their simple production, was acknowledged within a characteristic domain driven by its proper laws. This presupposed a conception of generation within the natural domain that was organized by forces and structures which operate beyond the single individual[20]. In other words, akin to the spreading of evolutionary theories, the idea of causal continuity between natural mechanisms of production and those pertaining to human generation has been essential as well as the specification and quantification of the mechanism of hereditary transmission. New contexts and enquiries had to be invented for investigating and interpreting form and function, matter and structure in a novel causal framework.

Interaction: when nature and nurture confound

A clear-cut shift in the definition of causality from qualitative and pluralistic influences described in the humoralist paradigm to the

ideal of one linear causal determination can be underlined around the half of XIX century[21]. The diffusion of the positivist trend, spread especially by Claude Bernard's works and implemented by the experimental advances of bacteriology made by Koch and Pasteur, enhanced the concept of *isolation* of the cause, rather than *interaction* amongst an array of influences. This new experimentally-based model inaugurated a "novel era of medical causality"[22] and proposed the mono-causal and specific ætiological explanation to which we are used: one-cause, one disease, and possibly one therapy (also dubbed as "Magic bullets model")[23].

From an epistemological standpoint, the isolation of the cause in bacteriology reveals a parallelism with the materialization of the cause in heredity. As the historian of medicine Lopez-Beltran has outlined in his thorough research[24], three key events can be highlighted to explain this process. Firstly, the *specific issue* of *heredity* entered the scientific debate in the French medical academy at the very end of XVIII century within the debate between humoralism and solidism[25]. Secondly, the substantive *heredity* replaced the adjective *hereditary* and *hereditari morbus* in scientific discussions, consolidating the material notion of the metaphor of heredity raised by its ontologisation. Thirdly, the idea of *latent causality* of disease became compelling for acknowledging the variability and the indeterminacy of the effects visible at the level of the individual, families and sub groups of population too. Physicians became acquainted with "heritability" when challenging constitutional and familiarity characters, and especially when observing heritable diseases.

An explanation of this turning point is reckoned by Lopez-Beltran in the increasing number of available clinic data deriving from the process of urbanization after the French revolution. Along these lines, I wish to remark that the novel idea of heredity, as the transmission of form *through* matter from parent to offspring, was acknowledged within the dispute opposing a holistic and fluid medical paradigm to

a mechanistic and materially-based one. As underlined by the historian of medicine Grmek, humoralism vs solidism longlasting dispute prevented physical and chemical explanations to be conceived under one unique integrated framework[26]. Interestingly enough, along those years, a conceptual shift occurred within the embryological debate: *form*, as causality subject to disparate influences in the humoralist model, became *matter in-formed*, i.e. matter which forms itself, within the epigenetic paradigm.

In the early XX century, after the rediscovery of Mendel's works, the scientific notion of heredity was established with the Mendelian laws of inheritance and later exploited in Morgan chromosome theory of heredity. This complex multifaceted process has been studied in depth[27] and would not be touched here. However, the unequivocal shift in the hereditary debate from a plural system of causes and influences, mainly qualitative, to specific and quantitative causality could be spelled out especially in the light of the rising opposition of nature vs. nurture, introduced by the English polymath Francis Galton in the end of the XIX century.

The American psychologist Gottlieb underlined that *Galton's entire scientific career revolved about the measurement of nature and nurture*[28], outlining pioneering techniques and concepts such as normal distribution of traits and hereditary transmission of mental ability, especially through his famous twin studies. Briefly, according to Galton's analysis, at birth there is a great potential for change and development (reaction range), but afterwards in the competition between nature and nurture, nature proves the stronger[29]. However, Galton underlines that *the bulk of the respective provinces of nature and nurture are totally different although the frontier between them may be uncertain*[30]. This determines that at their boundary *the interaction of nature and circumstance is very close and it is impossible to separate them with precision*[31]. In other terms, *interaction raises complexity* rather than distinction and separateness of the elements.

The traditional epigenetic hypothesis explained heredity and the process of embryonic development as result of a unique causality: they were both embedded in the same epigenetic process from which the unformed matter begins its development, according to its specific level of biological organization[32]. Along these lines, T.H. Morgan, the American founding father of genetics, who was anti-preformist and a convinced epigeneticist, in his foundational analyses on heredity underlined that heredity and development should be intended as a whole identical process[33]. Very briefly, the revolutionary definition of the gene as the entity responsible of traits' transmission from parents to offspring, firstly described in Morgan's chromosome theory of heredity in the 1920s, made the debate twisting yet another time. Due to the extremely complex nature of embryonic development and inheritance studies, the more "elementary" mechanic of genes' transmission[34] was exploited and paralleled to biologists' atoms[35]. Since molecular biology great achievements in the half of XX century, the abiding notion of the gene established the concept of "internal" determination of hereditary transmission and development, loosening the action and reaction between individual development, environment and the multiple set of causalities crossing heredity and development, despite epigeneticists' best intent.

Gottlieb interestingly suggests that Galton's distinction between nature vs. nurture could be paralleled to the separation between the study of development and of heredity in late XIX century experimental embryology because both *did not center their attention on the interaction* (i) of nature and nurture and (ii) of development and heredity, respectively. This disciplinary gap affected developments in biology, neglecting important topics of research, recently raised again by evo-devo theories and epigenetics studies[36]. In other terms, *Developmental analysis begins where the nature-nurture debate ends*[37]. I shall underline that, on the other hand, the same gap limited the development of a specific inquiry of the complex cause of

interaction itself; especially an ætiological inquiry devoted to the complex nature-nurture interactions. Nature/nurture dichotomy underpinning the debate was essential for disentangling natural and material characters of heredity; however, it eventually compromised an integrated analysis of natural and cultural interactions.

Broken or complex causality? Facing proxy and distal gene-environment interactions

Notwithstanding its ubiquity in the debate, and without pretension to exhaustive coverage, I wish to call attention to the rising complexity of actual ætiology and causal determination within epidemiological studies. Since the beginnings of epidemiology a fundamental challenge was the assessment of the causal relation between an exposure and a disease outcome establishing "The proof and measurement of association between two things"[38] of which a key example is the relationship between smoking tobacco and developing cancer[39]. The association between the two facts may be apparent and due to confounding factors such as genetic susceptibility, and exposition to many chemical or physical cancerogens, eventually masking the causal evaluation. Reverse association/causation is a champion of these kinds of difficulties, i.e. the association between a selected biomarker and disease could rather be due to undiagnosed or early disease, being consequence rather than cause of disease[40]. Although multivariable statistical analysis has been implemented to reduce confounding, however at the bottom of all reasoning lays the "conceptual ambiguity" of the most common diseases mechanism (defining mediators and cofounders) which bounds statistical modelling too[41]. Moreover, a tension between probabilistic risk factors and deterministic causal mechanisms is pervasive in epidemiological explanations[42].

After Bradford-Hill's introduction in 1965 of the pragmatic criteria of causal inference in epidemiology, numerous proposals of causality emphasizing mechanistic, probabilistic and philosophical criteria

have been outlined[43]. As a matter of fact, causality in epidemiology is usually under attack. Statistical approach - the core of epidemiological analysis - is considered concealing the importance of causal biological underlying mechanisms, and statistical methods are judged as inadequate for proving a causal relationship in an association of factors.
The epistemological proposal that I wish to discuss here is that theoretical frameworks of causal complexity arose again because the isolation and the separateness of nature and nurture was found broken also in biology and medicine, affecting the ideal of linear-deterministic causality. Accordingly, the debate about causality hardened especially in epidemiology where the quest for criteria of strong causal correlation burst, and nature-nurture causes are purely interdependent. Indeed, in contemporary researches nature (gene) and nurture (environment), traditionally considered as two isolated causes, become mostly intertwined when dealing with common non communicable diseases such as non-Mendelian complex disorders like cancer, or cardiovascular events. Evidences of complex ætiology turned researches upside down: from focusing on isolated natural/cultural causes to focusing on how gene *and* environment interact. Along these lines, heritability represents the individual's array of actualized genetic potential, and different environments are different opportunities for genetic potential to be actualized[44]. Currently, epidemiology still lacks an explicit, shared, theoretical account of causation and even discomfort arises towards the concept of causation itself[45]. Indeed there is no room for traditional "monocausality" as no factor is both necessary and sufficient. *Nevertheless,* as underlined by the American epidemiologist Rothman, *researchers interested in causal phenomena must adopt a working definition*[46]. Rothman's first pie model in 1976 proposed that causality should be intended in terms of "causal component", result of multifactorial causal mechanisms combining multi-causality, dependence of the strength of component causes on the prevalence of complementary component causes, and interaction between component causes[47].

In this framework, it should be underlined that the notion of "interaction" rather than "cause" is becoming prominent. Especially, since new approaches in system biology, bio-medicine, post genomics and sociology are demanding entirely new causal theories where interaction is in the spotlight too.

The term "interaction" widespread from genetics to biomedicine refers generally to a strong link/determination between one fact and another (i.e. gene network, cell communication, pathogen interaction, etc.). In other terms, "interaction" is used when emphasizing the high complexity involved in processes where no strict linear determination between two factors can be pointed out. For instance these processes are often dubbed with the metaphor of the "causal web"[49]. One key example is "epigenetics" that in its original meaning referred to the interaction, or cross-talk, between the genotype and the phenotype[50]. Epigenetic mechanisms, reversing the one-way genotype-phenotype relation, recently have been even said *to bridge the gap* between nature and nurture[51].

Actual medical genetics researches deal mostly with non-monogenic diseases, polymorphism and individual variability. The pervasiveness of the notion of *individual variability* in genetic studies called increasing attention to the fact that *variation is the new norm*[52]. An attempt of integration has been recently proposed in the "expanded environmental genomic disease paradigm"[53].

Genetic epidemiological approaches, such as Mendelian randomization (MR) are revealed as essential findings for evaluating causal inferences and establishing ætiological associations[54]. However many fundamental issues are still debated due to complex and entangled factors, such as the majority of disease without specific genetic loci and unexplained variability, or complex phenotypes and rare variants among population subgroups. Briefly, in MR even more extensive assumptions are required than in randomized controlled trials[55]. According to the epidemiologists Vineis and Kriebel, among all the

general issues to be faced there are genetic susceptibility, probability vs biological plausibility, time evaluation in the causal chain of ætiological factors, individual vs population level of observation[56].
The ætiological epidemiological baseline extended mono-causality into to the "determinants of health and disease" (behavior, impacts of environment, genetic and social determinants)[57]. Moreover, these interwoven factors evolutionary interacted both at individual and population levels revealing in their turn distal, more complex, "drivers of health and disease"; at the same time new phenomena such as globalization, climate change and urbanization are looming in. All these emerging complex phenomena suffer from classical categorizations. Three main new conceptual categories are considered: dynamism (time lags between exposure and disease, cumulative exposure, time-laden), multi-scale (personal scale, governance level), and cross-boundary (international, glo-cal)[58]. Multi-scale health challenges require the development of cross-sector and cross-disciplinary studies, and new technologies adequate for analyzing, and interpreting this complex spectrum of determinants of health and disease.
In conclusion, another essential issue should be mentioned enriching, yet complicating, the debate on causality: the "H" (human) factor. Biases inbuilt in human cognition and strategy-making as well as social and economic constraints are all inherent to the very construction and functioning of scientific enterprise (reward system of science). John Ioannidis, wellknown for his most cited article about scientific biases, presented in July 2015 the 24th Bradford Hill Memorial Lecture, "Exposure-wide epidemiology: revisiting Bradford Hill". He showed the results of a study where 40/50 of cooking ingredients randomly selected in a book of recipes have been found associated in the literature with either increased or decreased cancer risk[59]. After the review of each of Bradford Hill's nine criteria for causal correlation, Ioannidis stressed that *as Bradford Hill wisely suspected, none of the criteria has absolute value on its own. In the current research environment, several of the*

criteria have little predictive ability for causality; some even decrease the probability of causality. It should be remarked that obviously the criterion of "specificity" (i.e. one cause leading to one single effect) is comprised in the criticism. Nevertheless, if present causal criteria cannot inform the validity of inferences because no possible selected criteria are found to assess the *universal validity* of evidence, as underlined by Rothman, *scientific evidence can usually be viewed as a form of measurement*[60]. That is why keep improving empirical meta-research studies in order to thoroughly monitoring and assessing causal evidences is indeed the most convenient strategy, as Ioannidis strongly recommends.

Conclusion

The concept of cause was reviewed throughout some case studies in the history of ætiological models interweaving heredity with the analysis of environmental factors. Starting from the coalescence of nature and nurture in ancient and modern paradigms the article discussed how causal heredity and environmental factors disentangled and changed through times. This analysis revealed three main eras in medical causality (ancient, modern and contemporary) and two fundamental notions correlated with that of cause: influence and interaction. The notion of influence seemed more suitable for defining the porous causal relationship between individual and environment delivered by the humoralist tradition. On the other hand, according to contemporary western viewpoint the concept of influence rather than cause better tolerates also qualitative aspects within ætiological explanations.
Only recently, the concept of interaction boosted in biomedical and epidemiological approaches, leading to the reversal of the traditional dichotomy nature vs. nurture by looking at their interaction, especially at the interaction between individual, genetic, variability and environmental variability. Notwithstanding actual tremendous genetic and statistic advances, epidemiology meets a "broken" mechanism in establishing clear-cut ætiological correlation

in most common diseases where plural, complex causality occurs. Ætiological mono-causal explanations are challenged by individual variability and multiple probabilistic pathways and interactions. Time is to face novel methodological as well as theoretical proposals about causality tackling multi-scale challenges deriving from a globalized and complex world of interactions, human biases and ideologies.

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