THE MEANING OF ARISTOTELIAN CAUSATION FOR MOLECULAR ERA MEDICINE & PUBLIC HEALTH

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ABSTRACT. *To date the BioCosmological debate has turned on the notion of a personal functionality that human beings are born with and which defines their individual potentials and disease susceptibilities, but it is unclear how the functionality comes about. Generally it is appreciated that as they grow and opportunities open up, people may overcome initial biological hardships and rise up the ladder from physical needs to address the array of social demands they experience, ultimately driving towards some form of self-realization if prior demands have been satisfied. Foundational models of health inevitably beg the question of how whole person functionality comes about – from the ground up via ingrained mechanisms of healthy development, or by the person seeking means to satisfy their own purpose.*

To address the question of personal realization and how it can be furthered through medicine and public health, it is helpful to embrace both classical wisdom – the Aristotelian causes – and modern systems-level biology. In doing so, the need arises to go beyond simple monolithic views of mechanism. A focus on Aristotelian formal cause, for example, will lead to knowledge of a person's genetic makeup and genetic mutations, both of which outline various psychobiological strengths and weaknesses detected via genetic testing. The modern correlate of final cause or telos might look at various developmental constraints on the species or individual. At the prenatal level, the developing individual is bombarded by both positive and negative nutritional and stress-related factors. The effect of these impacts unfolds once the individual is born and later in life in terms of susceptibility to chronic illness.

Modern medicine and public health are currently moving in unparalleled directions – taking into account the whole genome and total environment – that are making the next phase of "medical" (larger sense of the term) development possible. In an inexplicable way, the stream of developments is presaged and described by the four Aristotelian causes placed together. One's telos is defined by one's genetics and environment working together towards a common end – personal fulfillment. Many health obstacles block the way. Modern meets classical to outline the layers of mechanism involved in human genesis, health and disease, and to show what kinds of tests and treatments will become possible in a revolutionized era of medicine and public health.

KEYWORDS: *Aristotle, Causation, Genetics, Genetic Testing, Molecular Therapy, Medicine, Public Health, Cancer, Apoptosis*

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Introduction: Where Does Cause Come From?

The world, as Norse, Greek, and Biblical mythology would have it, was created out of chaos. The pre-Socratic philosopher Heraclitus described the world as a fire alive that is never extinguished, and as a perpetually moving river that never ceases. Wrote the Greek epic poet Hesiod, "In truth at first Chaos came to be, but next wide-bosomed Earth" (Parada and Förlag, 1997). Aristotle, being aware of the poet's writings, commented, "Hesiod too might be held to have given a correct account of it when he made Chaos first … For that without which nothing else can exist, while it can exist without the others, must needs be first" (Aristotle Physics IV, 208b, Ibid.).

However, the reign of chaos does not exclude the appearance of activity in the universe, however. Objects, once they have come to be, have the capacity to induce change in other nearby entities. *Dunamis*, according to Aristotle, is the power which enables objects to exert themselves upon each other. The exercise of such power is *kinesis* – a movement or process (Metaphysics IX.1, 1046a12 in Cohen 2012). *Dunamis* may be considered in the sense of potentiality, such as the capacity of a woodcarver to fashion a block into either a table or a set of bowls. But it may also be viewed in terms of actual transformation, via *energeia* or *entelecheia*, into a more complete state (1048a25). The matter, or wood, is linked with nascent potentialities; the substance, a bowl or table, is associated with actuality.

Dunamis then would seem to admit order out of chaos, in both its actual and potential senses. Aristotle goes much further than this primary level of explanation for change, which ferrets out how the simple universe comes to be, when he launches into a description of cause or *aition* in Metaphysics I.I. In a sense, *dunamis* is a set-up for the notion of cause, since one variant deals with the material nature of an object, and the other with its form. In this paper we will consider the notion of causality in the modern context – the contemporary health sciences – and in the classical context – Aristotelian philosophy. Despite the earthshaking discovery of DNA, the basis of life, by Watson and Crick in 1953, science is still coming to terms with just what life

means. The wisdom of ancient philosophy can be quite helpful in parsing out the levels of causality in biology. Because biological science is the root of the health sciences, an expanded notion of its causal implications can have meaning for the types of health-conferring human interventions that operate at diverse causal levels. There is a chronology to the unfolding types of interventions that medical science has made available, so that the history of the health sciences, as exemplified by BioCosmology, also enters into the scientific and historical picture.

1. The Twinning of Scientific and Philosophical Perspectives

The health sciences are very much a program of explanation and control, an attempt to wrest order out of chaos (Verschuuren 1986, p. 97). These explanations are aimed at applying what has been inferred as a general law, that when X occurs, Y will follow. When sodium channels open and close, potassium ions will rush out, leading to heart repolarization detectable by electrocardiogram. When a heart beats, blood will eject from the atria and ventricles; sounds detectable by stethoscope will follow. These generalizations are the grist for the mill of science, allowing for both causal explanation and prediction.

One complication is that the causal laws being inferred cannot be separated from the factual statements surrounding the circumstances:

> *Asking "why" humans have an appendix one could get many answers. An embryologist would mention causes like genes and inductors: a physiologist might refer to functions like digestion; a paleontologist may talk about data from the previous phylogeny. Maybe it is better to talk about law-like implications instead of laws; and it is the hierarchical structure of a conceptual system which determines how law- like implications can be used in explanations (Verschuuren 1986, p. 98).*

This passage reveals the notion that causal laws in biology pertain to different levels of explanation, and that a network of concepts, not a flat intellectual plane, may be required to fully describe them. If one hones in on the distinguishing terms – "inductors", "functions", and "phylogeny" – it is quite clear that different categories of explanation are being invoked.

Verschuuren uses the heartbeat example to begin to differentiate the descriptors of different levels of physiologic explanation:

> *The relationship between beats and sounds can easily be seen as a causal one: the beats produce sounds. But the relationship between beats and circulation is peculiar: surely, it is causal (the beats make the blood circulate), but there is more. Biologists tend to say that the beats are there 'in order to' have circulation – and this is called a functional relationship. Functional relationships are causal, but causal ones are not always functional (Ibid., p. 102).*

Functional relationships are one type of causal relationship. Functional biology, concerned with how biological structures operate and interact, is an important field in modern biology alongside evolutionary theory (Mayr 2007, pp. 50-1). Inducers and functional mechanisms are already part of the modern biological panoply. The array of causal relationships can be taken in several possible directions from here. The author of the heartbeat example uncovers further layerings of causal relationship in a subjective direction. In this logic, functions are superseded by motives and intentions, which ascribe the fulfillment of an action to more than natural selection, with overarching actions being ruled by values, which mediate the appropriateness of the latter (Ibid., pp. 108-9).

Few modern participants in biological science, medicine, and public health would differ on the importance of values in the numerous examples of health and disease which arise and that demand attention. However, it might be productive to examine causal pathways by means of objective explanations and mechanisms before introducing more complex subjective levels of explanation. In Physics II, Aristotle offers his classic four-fold model of causation (Physics II.3 in Bambrough 1963, p. 214):

(1) Material cause: "that out of which a thing comes into being and that which remains present in it." Examples: bronze in the case of a statue, silver in the case of a cup.

(2) Formal cause: "the form and pattern are a cause." Examples: In the case of an octave, number in general, and more specifically, the ratio of two to one.

(3) Efficient cause: "the proximate source of change or rest: that which produces is the cause of what is produced." Example: a father and mother are the cause of their child.

(4) Final cause: "the cause insofar as it is an end; this is the purpose of a thing." Example: health is the cause of a person's going for a walk – a person goes for a walk for the good of their health.

Aristotle's father was a member of the guild of Asclepiadae, and his mother was a member of the Asclepiad family (Modell 2010, p. 411). It should not surprise us, therefore, when he mentions the intermediate states that arise through the agency of other medical techniques – slimming, purging, drugs, and surgical instruments – all having the same purpose, health, as their cause.

The preceding notions of inducers and functions ostensibly have a resemblance to Aristotle's efficient and final causes. Intentions are absorbed into final causes as well. One can read modern biologists trying to explain the behavior of an organism, and after distilling the explanations to their basics, the train of thought often turns out to be very similar to what Aristotle held 2,500 years ago. Ernst Mayer asks: What is the cause of bird migration? (Mayr 2007, p. 52). He actually gets more specific, pondering why a warbler in his summer place in New Hampshire starts its southward migration on the night of August 25th. Put so exactly, one imagines this particular act of migration must have an exacting cause. Mayr contends, though, that the cause of the migration is more complex than initially supposed, and requires weighing of four equally legitimate causes:

(1) Ecological cause: The warbler depends on insects for its nourishment, and would starve if it tried to winter in New Hampshire.
(2) Genetic cause: The warbler has acquired in the course of evolutionary history the proper genetic wiring to prompt it to respond appropriately to seasonal stimuli from the environment, leading to migratory behavior.
(3) Intrinsic physiological cause: The warbler flew south because it responded to the decrease in day length when the number of daylight hours dropped below a certain level.
(4) Extrinsic physiological cause: A sudden cold air mass, with northerly winds, passed over the author's area on August 25th, prompting an already eager bird, physiologically ready to migrate, to take flight.

Mayr's four-fold scheme provides useful signposts for causal theory in modern biology. The scientist further breaks these four specific causes into more generalized categories. The physiological readiness and conditioning of the warbler, interacting with photoperiodicity in daylight hours and the drop in temperature, constitute *proximate* causes of migration. The lack of food during the winter and the genetic disposition of the warbler are the *ultimate* causes (Ibid., p. 53). Mayr argues that proximate causes govern the responses of the organism and its organs to factors in the environment, while ultimate causes are responsible for the evolution of the particular genetic program with which every member of the species is endowed. Many heated debates between biologists trying to get to the bedrock "cause" of a certain biological phenomenon could be cooled by realizing that one of the opponents is concerned with proximal cause, while the other is concerned with ultimate cause.

In BioCosmologic scholarly debate, opponents have likewise sided with teleological, final cause-based explanations of organismic microevolution versus efficient cause-based explanations (Khroutski 2007; Modell 2006). It is important to see the hand of Aristotelian thought subliminally guiding the shape of these arguments, which comprise a logical continuum. Really, a further plumbing of the meaning of biological causation, using Aristotle's scheme as a template, is called for.

2. The Meaning of Aristotelian Causation for Modern Biology

A. Efficient Cause in Biology

To institute a modern rendering of Aristotelian causation, it is helpful to see the role of efficient cause as it operates at the cellular post-translational level, once the genetic machinery has already generated a protein involved in metabolism. Most modern biological explanations of metabolism and its disruption depend on step-by-step accounts of one molecular complex acting on another, often with the mediation of enzymes such as kinases and phosphatases. Through the latter, energy rich adenosine triphosphate (ATP) releases an inorganic phosphate molecule, liberating energy which carries a protein substrate to the next step in a biochemical pathway. The pathways followed can be quite extensive, and can also involve forks that lead in either constructive or destructive directions. These courses of action, which can be

both linear and circular with feedback steps, are the very picture of Aristotelian efficient cause.

The 76-amino acid protein ubiquitin is acted upon by ATP conversion in several steps, ultimately leading to the degradation of a much larger protein substrate (Vucic 2011, p. 439). In step 1, activation, ATP releases two phosphates to power the transfer of ubiquitin to an E1 enzyme. In step 2, conjugation, the activated ubiquitin is transferred to an E2 enzyme. In step 3, ligation, the E2 enzyme carries the ubiquitin to an E3 enzyme, which ligates or attaches ubiquitin to a recipient protein. Scientists are aware of tens of types of E2 enzymes, and hundreds of E3 varieties. The process of ubiquitin addition can occur multiple times, leading to the construction of a polyubiquitin chain, or, conversely, to a reduction in chain size. The nature of the lysine (amino acid) residue on the ubiquitin chain decides the fate of the recipient substrate protein. Given one type of lysine residue, the recipient protein will be tagged for degradation into smaller peptides. Given another type, the protein will go on to form cellular signaling complexes (Ibid., p. 440).

Ubiquitin can also be involved in much broader processes that lead to cell survival or death. Several ubiquitin ligases (the third step above), abbreviated FBW7 and MULE, promote programmed cell death (apoptosis) through their E3 ligase activity (Ibid., p. 441). Others, the IAP ("inhibitor of apoptosis") proteins, block cell death. An increase in the level of IAP proteins in tumors, and their engagement in cell signaling pathways, implicates them in the genesis of human malignancies (Vucic 2013, p. 448). Scientists reflecting on biology in a philosophical way have noted the profound role that mechanisms like oxidation and apoptosis can play in the balance of life and death. Cell death can be very important in normal (the removal of surplus cells in neurogenesis; the development of hollow organs such as the heart) and pathologic circumstances (parasite killing, e.g., malarial infection; tumor suppression and malignancy) (Eze 2014, p. 210-11; McPhate 2014, p. 222). In its most expansive sense, molecular participation in the life-death equation plays into the preservation of the species, and to some symbolizes the religious antinomies of self-transcendence and self-annihilation. In the scientific sense, though, it represents the chain of efficient cause that leads to protein and cell life and death and the business of cellular metabolism.

B. Formal Cause in Biology

Biological pathways are the result of evolutionary forces that have allowed one type of mutation to thrive, another to perish. The forces at large involve natural selection, migration of individuals from one population to another, and genetic drift (Bodmer and Cavalli-Sforza 1976). Each of these forces acts upon a mutation that has spontaneously arisen. Aristotle recognized the existence of spontaneous events, whose cause is external to the event itself and which by definition do not occur for the purpose that visibly follows the event (Physics II.6 in Bambrough 1963, p. 221). In philosophical terms, mutations may be thought of as occurring in and of themselves, not via the genetic effects they engender. However, what derives from the initial mutation – the production of a protein – typically follows a genetic

sequence that may be likened to a formal cause presiding over a mechanistic train of events.

Malaria is endemic throughout Central Africa and southern regions of the Middle East and Southeast Asia. Its agent is the *Plasmodium falciparum* protozoan parasite, and the Anopheles mosquito is the vector that carries it. The story does not end there, however. The distribution of the hemoglobin-S gene follows a very similar worldwide distribution (Bodmer and Cavalli-Sforza 1976, p. 310). Studies have shown that children with genes for *HbAS* (1 typical hemoglobin gene copy; 1 sickle cell gene copy) and *HbSS* (2 sickle cell gene copies) have significantly fewer episodes of severe malarial anemia than children in the first five years of life with *HbAA* (Aidoo et al. 2002, p. 1311-2). *HbAS* is further associated with protection against all-cause mortality in children during the period when they are most at risk for severe malarial infection. Despite the detrimental effects of a double dose of the hemoglobin S gene, it has been found to be in population equilibrium in those areas where it confers a protective advantage, which is in essence the type of patterning – at the personal and population genetic levels – Aristotle cited when he discussed formal causes.

Why does hemoglobin S carry a protective and, therefore, evolutionarily selective advantage? Hemoglobin S tends to crystallize at the low oxygen tensions found within narrow blood capillaries (Bodmer and Cavalli-Sforza 1976, p. 311). The crystallization and consequent blood cell membrane sickling lead to a tendency of the red blood cells to break open or lyse, the source of the anemia. The *falciparum* parasite, which occupies red blood cells and draws nutrients from them, is hindered by these conditions. The formal cause of sickle cell anemia may be equated with the evolutionary benefit to populations possessing the hemoglobin S gene, and individual benefit to those persons with sickle cell trait (i.e., *HbAS* individuals).

For a more recent biological example of formal cause, consider the CCR5-delta 32 cell surface receptor mutation, known to result in almost complete resistance to HIV-1 infection and AIDS. The mutation has geographic attributes, with a prevalence of 14-18% among certain Eurasian northern populations, and a gene frequency that shows a declining north-to-south gradient. Early studies suggested these population changes did not come about by genetic drift, the more likely explanation being one of selective advantage following a catastrophic epidemic occurring between 275 and 1875 years ago. Many scientists believe the Black Death of 1348 (the "Great Mortality") was responsible for the propagation of the mutation, though rival hypotheses also hold out the possibility of smallpox or a hemorrhagic disease such as Ebola virus being the culprit (Cohn and Weaver 2006, p. 497-8). So an evolutionary explanation, even if it is pluralistic, exists for the spread of the mutation.

The HIV virus needs the human chemokine cell receptor CCR5 to infect CD4+ T cells and manifest AIDS. With a CCR5-delta 32 mutation in the person's genetic constitution, the HIV virus lacks a way of entering the T cell due to a paucity or absence of the necessary cell surface receptor. In the mind's eye one can visualize a virus approaching the cell, no CCR5 receptor sticking out of the cell surface, and the virus migrating past the cell with no means of attachment. It is very much a matter of

presence and shape – the proper configuration for the specific virus. A fortunate break for the bearer of this mutation is the result of formal cause, both at the overall evolutionary and the tinier cellular level.

C. Material Cause in Biology

The material cause is what constitutes the makeup of a given body. Health and disease are the properties of cells, tissues, and bodies within a material environment which is either health promoting or health deterring. Medical and public health researchers have long been concerned with gene-environment interactions which reflect the effect of the environment on gene operation. The environment may serve as a modifier in the same way that one's demographic characteristics (gender, race-ethnicity, height, weight) can modify health status – through statistical means. More recently, however, researchers have explored epigenetic effects of the environment, which involve transmission of environmentally-induced characteristics from one generation to the next other than through the germ line.

Lead toxicity is a prominent example of epigenetic mechanisms at play. Lead remains a ubiquitous, non-degradable toxic pollutant in the environment. Although in the USA it has been largely removed from paints and gasoline, it remains a serious problem since it can be found in products used daily – pipes, batteries, ceramics, water, food, and toys – and remains in lead-polluted soil. As of 2006, it has been estimated that over 275,000 children in the United States continue to have blood lead levels exceeding the Centers for Disease Control and Prevention (CDC) recommended limit (Pilsner et al. 2009, p. 1466). In developing countries, the prevalence of elevated blood levels greatly surpasses the United States in numbers, amounting to a global public health problem. Major health effects include spontaneous abortion, preterm and low birth weight deliveries, attention deficit hyperactivity disorders, reductions in childhood IQ scores, and (more speculatively at this point), increased deposit of beta-amyloid associated with Alzheimer's disease later in life.

The epidemiology, however, belies the equally important question of how lead operates to induce these consequences. Lead has been found to modify the activity of phosphatases in cell cultures of neurons, which could impact synaptic plasticity (Senut et al. 2012, p. 3). It is thought that lead can interfere with neurogenesis to reduce the proliferation, differentiation, and survival of newly generated neurons. Another prominent epigenetic mechanism, the addition of methyl groups to DNA sites called CpG islands, is also likely to be involved. Lead exposure inhibits the activity of IGF1-stimulated methionine synthase, involved in the regulation of DNA methylation in human neuroblastoma cells (Ibid., p. 6). Lead has been shown to decrease the levels of phosphorylated epigenetic regulators that bind CpG islands regulating the expression of key factors in synapse development. Lead-induced modification of the global DNA methylation landscape could, therefore, have an effect on the developing brain and more remote effects on the brain later in life.

Like lead toxicity, the epigenetics of cancer has been studied intensively over the last ten years. The International Cancer Genome Consortium's efforts have

yielded a catalogue of mutations in numerous epigenetic regulators of gene action. Clinical prevalence has come to be associated with the idea of causal relationship in this setting:

> *A central tenet in analyzing these cancer genomes is the identification of "driver" mutations (causally implicated in the process of oncogenesis). A key feature of driver mutations is that they are recurrently found in a variety of cancers, and/or they are often present at a high prevalence in a specific tumor type (Dawson and Kouzarides (2012, p. 14).*

The notion of "prevalence" is linked with "strength of association," which is a factor in statistical inference distinguishing causality from association and spurious correlations (Weed 1988, p. 20). Missing is the array of environmental risk factors that play into cancer genesis, and which may directly or indirectly induce such mutations: breast cancer – radiation exposure, alcohol, obesity, early menstruation, late onset of menopause, never having been pregnant, and postmenopausal hormone therapy; colon cancer – low-fiber, high-fat diet, radiation therapy, alcohol, tobacco, sedentary lifestyle, obesity, and diabetes. The cancer story goes substantially beyond statistical associations to those risk factors now identified as material causes of cancer.

Epigenetic mechanisms are particularly susceptible to environmental influences. The most widely affected epigenetic pathways involve mishaps in histone acetylation and methylation, i.e., in addition to those proteins known to coil DNA. Altered expression of several histone lysine acetyltransferases has been observed in a range of cancers. A number of viral oncoproteins (cancer proteins) are associated with these alterations, making viruses an environmental cofactor (Dawson and Kouzarides 2012, p. 17). Histone lysine methyltransferases, in contrast to their acetyltransferase counterparts, tend to be highly specific enzymes that target particular lysine residues. An emerging area of interest right now is the role of catalytic components called EZH2 in complexes that methylate histones (Ibid., p. 19). Overexpression of EZH2 confers a poor prognosis in breast and prostate cancer. Methylation changes in cancer also occur in sites other than histones. CpG island methylation is commonly altered during malignant transformation. Studies have shown that 5 – 10% of normally unmethylated CpG DNA promoter islands become abnormally methylated in a variety of cancer genomes (Ibid., p. 15).

Many other disease conditions are the result of epigenetic mechanisms. What they share in common is the tendency to be highly influenced by environmental factors, and the ability to be transmitted from generation to generation other than genetically (Saniotis and Henneberg 2013, p. 13). Lacking a genetic basis, these mechanisms cannot be considered formal causes of disease. They serve as the material basis of disease, and a prime focus of research in the molecular genetics era.

D. Final Cause in Biology

Final cause according to Aristotle is concerned with the end or purpose of a thing. Biological functions as discussed earlier are a good example of final causes. In maintaining the smooth running of individual organs and systems, they allow the individual as a whole to walk through life and accomplish his or her goals. Khroutski has argued that every living subject has "the basic cosmist functionality" (BCF). An individual's life is "intrinsically and basically dedicated to the ultimate realization and execution of their definite function" (Khroutski 2014, p. 267). Life follows a progression, starting as Maslow suggested with the satisfaction of physiological and physical needs, and moving ultimately towards the satisfaction of aesthetic need and self-actualization.

It is possible to see an individual's genome, their entire genetic constitution, as setting the limits on what they are capable of. For example, a male with the genotype for predominance of fast-twitch muscle might have the capacity to become a great sprinter, while a female with predominance of slow-twitch muscle might become an historic distance swimmer, like Diana Nyad. Indeed, companies now offer genetic tests to determine a youngster's genetic status for the ACTN3 gene variably linked with these two varieties of muscle. However, genetics is not destiny. In fact, ACTN3 explains just 2-3% of the variation in muscle function in the general population. Many other genetic and environmental factors are responsible. On the other hand, it must be borne in mind that an individual is not like a genetic test. Genetic tests check the status of a single gene or a handful of genes. An individual is a complete package – all the genes which serve a major function, a minor function, which interact with other genes, and which are in the process of interacting with the environment are already present. That the function of these myriad genes cannot be fathomed does not mean they do not have a function. Their totality combined with the body's response to the surrounding environment does have a major impact on the individual and his or her talents, susceptibilities, and dispositions.

Fetal environment also matters. Exposure to stressful life events among African American mothers during pregnancy has been found to increase the likelihood of fetal growth restriction and preterm birth. Maternal insulin resistance, hyperinsulinemia, and diabetes during pregnancy can abet the passage of glucose and insulin across the placenta, increasing the chances of a similar state of weight gain and diabetes in the progeny (Kuzawa and Sweet 2009, pp. 8, 9). A person born with Down syndrome, having an extra copy of chromosome 21, will encounter definite limitations in school and in job life. Of course, the overall gestalt of characteristics making up the individual and opportunities presented to them will influence the quality of life they experience. Special education in school and open door policies in the workplace can create a meaningful life for these persons. Overall, genetics and environment early in life, including prenatally, can have a profound effect on the individual from the point he or she is born.

This position is not to forget positive and negative influences on one's health as life progresses. The weathering hypothesis contends that repeated stress and other health insults can accumulate and increase disease vulnerability across the life course

(Geronimus 2013, p. S56). In a study of white mothers mean age 38 years who were more or less stressed depending on whether they were caring for an autistic child, those facing the demands of care giving for an autistic child had shorter telomeres (a genetic proxy of aging) than those who did not (Ibid., p. S60). Black women in highly segregated urban areas enter adulthood in different circumstances than their youth. Many studies have found them in their 20s, 30s, and 40s as primary caregivers of needy children and ailing or disabled peers and elders (Ibid.). Life presents demands that can derail a person from whatever basic functionality they may otherwise have followed. We are presented with diametrical stories of what may happen. On the one hand is the legend of John Henry, an African American thrown into a Virginia penitentiary and tasked with hammering a steel drill into rock to make holes for explosives to blast it away. His fortitude is measured in a race against a steam powered hammer, which he won right before his heart gave out from stress (Levine 2007). On the other is the story of Philip Carey in W. Somerset Maugham's sensational novel *Of Human Bondage* (Maugham 1992). Carey encounters impediments early in life – he is born with a club foot and his widowed mother dies when he is nine. Despite ups and downs in his younger occupational life and failed romances, educational and financial resources made available to him by a caring aunt and uncle enable him to study medicine and become an admired doctor caring for humble folk in the English countryside. Both individuals develop the talents with which they were born to a notable extent, but a marked difference exists in how long and in what emotional climate they find purchase to practice those talents.

The life course, then, would seem to be equally as important as early life conditions in governing the full attainment of one's basic cosmist functionality (Geronimus 2013, p. S56; IOM 2003, p. 52). No doubt genetics are a fundamental determinant of the physical and mental boundary conditions of the BCF. Its character reflects life activity that an individual is uniquely suited to fulfill, but as a final cause of the ordering of various enabling factors, it is a very complex biological entity.

3. Therapies Crisscrossing the Era of Molecular Genetics

We are now in a position to take a look at therapies addressing the various levels of biological causation and their fit into the timeline.

Normal regulation of ubiquitin-modifying enzymes is altered in cancer genesis. IAP proteins interact with ubiquitins but because they are inhibitory, increase the likelihood of malignancy. Scientists have developed IAP antagonists that block IAP protein interactions while activating their ubiquitin E3 ligase activity, thus inducing cell death – apoptosis – in tumor cells (Vucic 2011, pp. 448-9). A second approach has been to develop drugs that antagonize pro-inflammatory tumor necrosis factor receptors (TNFR1 and TNFR2) which promote tumorigenesis. These pharmaceutical compounds are small molecule antagonists that bind to aberrant proteins hindering cell death. Such compounds are on one end of the R&D continuum that may be thought of as starting with the development of one of the earliest marketed anti-inflammatory medications – acetylsalicylic acid, or aspirin. Salicylic acid was discovered by Edward Stone in 1763. He extracted this active ingredient of aspirin

from the bark of a willow tree. At approximately the same time, in 1785, William Withering first described the anti-arrhythmic properties of digitalis, extracted from foxglove. This time period is generally considered to be the beginning of modern therapeutics. One can set the timeframe for the development of compounds that work through blocking biologic pathways (i.e., chains of efficient causation) as stretching from 250 years ago to the present.

Slightly earlier, in 1672, Robert Talbor cured King Charles II of "ague" (malarial fever) by infusing cinchona, whose active ingredient is quinine, in white wine, which would set the time clock on modern therapeutics, or perhaps what are now considered patent medicines, a bit earlier. It is thought that quinine functions by facilitating the buildup of cytotoxic heme in parasites. The heme accumulation leads to the death of the parasite. Crude work on malaria vaccines began thirty years ago, quite a while after Edward Jenner's testing of cowpox vaccine in 1796. Volunteers were intentionally given repeat bites by *Plasmodium falciparum*-infected and irradiated mosquitos. Over the last ten years the vaccines have become more specific, targeting *P. falciparum* surface antigens at various stages in its life cycle (Arama and Troye-Blomber 2014, p. 459). Immunogenicity is enhanced by creating recombinant proteins linking *falciparum* surface antigens with other surface antigens such as from hepatitis B. These techniques constitute a formal causation approach in that the antibodies selected for structurally complement the specific antigens being injected.

Vaccines for the prevention of HIV have not yet reached the efficacy stage. The goal is to develop HIV envelope structure immunogens that tightly bind neutralizing antibodies. Vaccine design is based on visualization of the viral antigenic scaffolding and core structures involved in binding with the antibodies (Ahlers 2014, p. 187). An alternative scenario is to block HIV linkage to T-cell surface receptors. Maraviroc, a small molecule CCR5 antagonist, performs this function and has been U.S.-Food and Drug Administration (FDA) approved (Wilkin and Gulick 2012, p. 83). A variant of this alternative approach is to block production of cell surface receptors at the gene level. Researchers have used a type of enzyme called a "zinc finger nuclease" to bind to a specific 12-base pair sequence in DNA and cause a double-stranded break in the portion which codes for CCR5 receptors (Voit et al. 2013, p. 786). While both techniques have been shown to confer significant levels of protection, they fail for those viral strains which can adapt by using an alternative receptor for insertion, CXCR4. Hygienic prevention remains the ideal approach for HIV infection, but short of that, many antiretroviral drugs and combination regimens are available. Antiretroviral drugs operate by blocking the reverse transcriptase enzyme's functioning, preventing production of virus double-stranded DNA from the original viral single-stranded RNA. The first FDA-approved drug of this kind came out in 1987 – zidovudine (Retrovir) – now more than 25 licensed drugs that block HIV replication are available (Maartens et al. 2014, p. 4). This assortment of approaches, from vaccination to disruption of DNA transcription and viral RNA translation, reflect at various levels of depth the Aristotelian view of formal cause. They affect pattern and shape at the tiniest of levels. Historically they reach back centuries, but the more contemporary interventions have only emerged in the last 25 years.

Material causes of disease have classically been approached through control of environmental offenders, though in the molecular genetics era it is possible to check and in some instances treat for epigenetic effects adversely affecting gene expression. The virtues and drawbacks of lead have been known since Roman times (images of the Roman patron saint Vulcan displayed several features of advanced lead poisoning – lameness, pallor, and wizened expression). Despite the highly touted introduction of tetraethyl lead in the early 1920s, cumulative evidence of its harmful effects forced its inclusion in the Clean Air Amendments of 1970 – a public health policy approach. In 2009 Pilsner et al. used the pyrosequencing technique to measure DNA methylation from lead in maternal bone and cord blood (Pilsner et al. 2009). Measurement in inaccessible tissues poses difficulties for intervention in populations suffering environmental impacts. Public health techniques for predicting target tissue methylation at CpG sites from more accessible proxy tissues are now being developed (Maartens et al. 2014).

The U.S. FDA has now approved four drugs – given clearance between 2004 and 2009 – designed to interact with the epigenome to manage cancer in the clinical setting (Mummaneni and Shord 2014, p. 496). Two are DNA methyltransferase inhibitors; two are histone deacetylase inhibitors (see **3.**C.). Epigenetic markers are currently being used to enable personalized tailoring of conventional anticancer drug use. However, these new drug classes which impact the epigenome directly affect multiple targets, making it difficult to conduct testing to predict benefit ahead of drug use. It bears repeating that the epigenome modifies gene action; it is not permanently coded in the sense that DNA, and can undergo change in the course of a lifetime. Revolutionary changes have occurred in this area in the last ten years which address the environment at large and the inner environment, the latter being sensitive to the former. Epigenetic modifications reflect material causation impacting health.

Molecular era interventions representing final causation would influence the fruition of a person's capabilities and prevent impediments that block this fruition. They would be both mental and physical. On the impediment side, genetic testing for Apo-E genotype, one predictor of late-onset Alzheimer's disease, became available in the mid-1990s. At that time professional organizations believed the test was not ready for widespread use. In 2007 the European Federation of Neurological Sciences and the Canadian Consensus Conference on Diagnosis and Treatment of Dementia produced systematic recommendations describing rationale boundaries for use of the test (BCBSA 2012). A year earlier a patent was granted for the use of ACTN3 genotype screening in assessing muscle type for athletic performance. Atlas Sports Genetics, not without controversy, placed the test on the market in 2008 (Lite 2008). These kinds of tests offer a skeletal reflection of human ability, especially since so many factors are involved in the items for which they test.

As of 2013, the U.S. National Institutes of Health (NIH) launched major, well-endowed initiatives to explore the use of whole genome sequencing in newborn healthcare and in more general patient care (NIH 2013a,b). In an interesting twist, the NIH in this same year began depositing the whole genome sequencing data from the Alzheimer Disease Sequencing Project into data repositories publicly available to the

research community. The result may be that shortcomings associated with any one genetic test predictive of Alzheimer's disease could be overcome by knowledge of the other genetic determinants of the condition. Whole genome sequencing might also be expected to show up for any one individual a host of incidental information on susceptibility for chronic conditions (cancers, heart conditions, diabetes) that could strike in mid- to late-life.

The realization of personal whole genome sequencing moves science a step closer to a forecast made by the U.S. Institute of Medicine in 2006:

> *New tools of analysis have made it possible to define and refine the idea of what personality traits actually are, and to demonstrate the universality of certain kinds of individual differences. ... Personality traits are consistent and are associated with behavioral trends, coping strategies, and health behaviors. This makes it possible to use them to predict health and life outcomes (IOM 2006, p. 77).*

It can be expected that knowledge of disease susceptibility genotypes made possible by whole genome sequencing will lead to prevention of risky behaviors that could block a person from reaching towards their life goals. In the intermediate term, whole genome sequencing may also turn up genetic loci indicative of human traits or capabilities, of which the ACTN3 locus is simply an early harbinger. Then the goal of determining a person's basic cosmist functionality and the means, health-wise, of fulfilling it will become a real possibility. Given a favorable environment, which is a societal decision, the technology – genetic and social – will enable the manipulation of final causes in the human biological domain.

4. Historical Fit of Molecular Genetics Developments

The four categories of Aristotelian causation fit the biological discoveries being made fairly well and without much strain. The classes of discoveries each have a penumbral origin dipping back into the history of conventional drug therapy, which began several centuries ago. The ascertainment of compounds from plants was a lasting gift from a more naturalistic, humoral era of medicine, Khroutski's 1st episteme. However, it should be noted that the Asclepian cult surrounding Aristotle's parentage believed that the role of the physician is to treat disease, and restore health by restoring imperfections caused by the accidents of life and birth (Greaves 2004, p. 136). This approach was a departure from the cult of Hygeia, which held that health exists in the natural order of things, and is an attribute to which men are entitled if they govern their lives wisely.

An Enlightenment fever for observation and application coupled with necessity compelled the discovery of vaccination around the same time as modern pharmaceuticals. Lack of a framework for the formation of environmental standards, and perhaps political will, held off any organized push to regulate the material environment. Development of prenatal and life course approaches took the longest to study and develop.

Outside the penumbra lies the era of molecular genetics. The order of discovery amongst the different interventional categories roughly flows from simplest mechanism to most complex. For the last category, representing final causation, it is even difficult to lay a finger on a single type of molecular genetics technology. A general overlap exists in the chronology of development from one category to another. Interventions using formal cause – medical manipulation by shape of the target and organization of the host genetic code – will naturally flow from those using efficient cause, and depend on the logic of efficient cause more or less. Functional medicine in the whole person sense will develop from and overlap those techniques that depend on material causation (the person's social-ecological environment is important; surveys and inventories to explore support and stress from the environment are valuable) (Khroutski 2007, p. 14; IOM 2006, p. 77). However, the epigenome is not organized the same way as the genome; it cannot be sequenced, at least not in one fell swoop.

The most comprehensive approach will, as Khroutski surmises, take into account a person's micro-evolution within the context of the macro-evolution of persons, culture, and ecosystem surrounding the individual (Khroutski 2007, p. 8). Each has its own driving force, making consideration of teleology, the inherent purpose of a system, a factor in its operation or well-being. *Telos*, or purpose, depends on *entelecheia*, or a power of completion (Ibid., p. 10). The two concepts are linked in terms of ordinate and superordinate. The Venn diagram of these types of discoveries is that of an ellipse within an ellipse within an ellipse, functional approaches being outermost, but with only about 80% shared overlap between each ellipse due to fundamental differences of emphasis in causal approaches.

The BioCosmological historic scheme is triadic, not four-fold (Khroutski 2014, pp. 280-1):

1st Episteme: Organismic, dealing with holistic, naturalistic care of the individual patient;

2nd Episteme: Organic-pathological, employing a pathocentric and statistical approach focused on cure of disease;

3rd Episteme: Cosmist, dealing with biological, social, and personal unity, and fit within macro-evolution.

Khroutski has likened the three epistemes to the Hegelian framework which is, indeed, concerned with the development of the individual and the world spirit as these ontogeneses gain self-consciousness through time (Hegel 1966, 44-6). Hegelian logic, likewise, is concerned with the next step in the dialectic between an original proposition and its contrary, a three-part movement overall (Ibid., p. 72; Khroutski 2014, p. 281). The framework is logical-historical, with completely non-overlapping, sequential phases. It should not be assumed that the types of discoveries made during a given period must have the same structuring as the period itself, since the intent of the two frameworks is different. Causal schemes are not historical but metaphysical, which Aristotle reasoned requires four levels of explanatory concept.

The 2nd, intellectually-oriented episteme in which we are now situated has thus experienced at least four overlapping periods of discovery corresponding to the four

Aristotelian causes, i.e., to the four types of general process which can be harnessed to cure and prevent disease. Khroutski asserts that each episteme contains a dualism (e.g., subject-object or patient-disease in the 2nd episteme). There is no argument here, especially since molecular genetic interventions relate patients to objective modes of diagnosis and treatment. Do practitioners in each of the epistemes employ an arsenal of approaches analogous to the levels of Aristotelian causation? Further medical-historical analysis is needed.

Conclusion: The Pertinence of Aristotle to the Modern Era

Two questions immediately arise when trying to apply an ancient Greek philosophical system to modern medicine:

(1) How could Aristotle develop a system that would be so widely applicable outside the metaphysical domain?

(2) How could an intellectual system about the everyday world apply to entities at the submicroscopic, genetic level?

With respect to (1), we should not underrate Aristotle. Not only was he a philosopher, but also a comparative anatomist who introduced systematic animal dissection into the Lyceum. He is known to be the author of the *History of Animals*, *Generation of Animals*, *Parts of Animals*, and a lost book on *Anatomai* or "Dissections" (Modell 2010, pp. 413-4). Little wonder that his metaphysical system applies to medicine. With respect to (2), Aristotle was a very talented observer. In Physics Book II he provides numerous empirical examples to back up his philosophical assertions. These examples range from the construction of a house to the art of shipbuilding to the makeup of a metal smith's products to the behavior of rain and growth of corn. He assayed the causal processes involved and exhausted the possible categories into which they fit. Tight logic was applied which overcome the differences of scale that occur in nature and which scientists observe today.

Young people often ask the question, "Are we there yet?". Has medicine yet arrived at the 3rd historic episteme? With the current emphasis on the life course in public health and personalized treatment in medicine, it is well nigh getting there. Suppose that all the current hopes of the researchers of the molecular genetics era come to pass. Whole genome sequencing becomes an everyday tool; behavioral genetic determinants are finally mapped-out; chronic disease drawing-board drugs win approval and direct gene transfer into the human genome becomes safe and secure; the human brain "code" becomes understandable so that we can link neural activity with cognition, perception, and emotion. Then where do we stand? Is this ideality the completion of the molecular genetics era or a new holistic beginning? All of this evanescent speculation is glitter compared to Aristotle's realization of the four levels of causation, which apply to Nature in all its passing transformations.

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