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A brief history of the natural causes of human disease

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Abstract

In the study of the causes of disease that have arisen during the development of humankind, one can distinguish three major perspectives: the natural, the supernatural, and the artificial. In this paper we distinguish the rational natural causes of disease from the irrational natural causes. Within the natural and rational causal approaches of disease, we can highlight the Egyptian theory of putrid intestinal materials called "wechdu", the humoral theory, the atomistic theory, the contagious theory, the cellular theory, the molecular (genetic) theory, and the ecogenetic theory. Regarding the irrational, esoteric, and mystic causal approaches to disease, we highlight the astrological, the alchemical, the iatrochemical, the iatromechanical, and others (irritability, solidism, brownism, and mesmerism). (Gac Med Mex. 2015;151:749-61)

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Introduction

Ever since primeval ages and until the present day, both death and disease have drawn fears and concerns to humankind. Prehistorical and ancient human groups adopted a supernatural causal focus, specifically magical-religious, on disease. In fact, especially in prehistoric and antique times, disease was correlated with witchcraft, demons or the will of gods, since its origin was assumed to be supernatural. However, along with the cultural development of some civilizations, a naturalistic approach to the causes of disease gradually emerged.

When studying the causes of disease that have been proposed during the development of mankind, three large perspectives can be distinguished: the natural, the supernatural and the artificial approaches. Natural is to be understood as everything that exists independently of human beings, as opposed to that that exists artificially or as a consequence of human creation, and supernatural, is everything that exists beyond the natural world, secularly or religiously speaking[1]. The word *artificial* comes from Latin *artificialis*, the roots of which are *ars* ('art') and *facere* ('to make'); therefore, *artificial* refers to something "made by man"[2-6]. Consequently, every human, sociocultural act, implicitly or explicitly conventional is, at least partially, artificial.

With regard to the current debate on health and disease, two perspectives are basically distinguished: the naturalistic one, the argument of which is that the concept of health is neutral and objective, denying its quantitative conceptualization, and the normative one, where the concept of health is proposed as having a quantitative charge, since both diagnosis and treatment of a sick person are linked to a cultural and social

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context[7]. In this monograph, some of the natural causes that have been proposed throughout the history of mankind are briefly developed. Prior to this goal, it is important to briefly describe the historical process that enabled the development of a natural causal perspective of disease.

The transition of the supernatural conception of disease to the natural one is usually based on two historical facts: on one hand, the approach, in the ancient Egyptian civilization, approximately 5000 years ago, of the putrefied residues (*whdw*), and on the other, the influential work of the first Greek philosopher, Thales of Miletus (624-546 B.C.), who established the bases for the beginning of a new focus on the world. Indeed, the questionings on the nature of the world received mythical and religious answers until Thales of Miletus, when they become rational and natural[8,9]. Together with the work of Thales, the contribution of Alcmaeon of Croton (5th century B.C.), who did not make a single reference to the supernatural origin of diseases in his work, should also be highlighted. With these bases, on the 6th century B.C., Greek medicine was almost entirely transformed into a secular discipline that emphasized on observation and experience. Although pre-Socratic philosophers such as Empedocles of Agrigentum (492-432 B.C.), Diogenes of Apollonia (fl. 5th century B.C.) and especially Pythagoras (570-495 B.C.) have been proposed as possibly having influenced on the thought of Alcmaeon, the originality of his ideas has led many investigators to consider him as a figure independent of the Pythagoreans. His perspective contrasts both with abstract speculation and with the esoterism of the Pythagoreans. His work is considered a fundamental piece in the attempt to understand the *physis* and its disturbances by means of political concepts such as *isonomia* (equality of rights) and *monarkhia* (predominance of one over the others). In addition, the first manifestation of physiological pathology, which in disease is considered an alteration of nature's order, arises with his work.

Greek medicine possibly started developing from a fusion between the physiological ideas of naturalistic philosophers and the ancient practices of Asclepian priests. Therefore, Alcmaeon of Croton's meritable work is the foundation of Greek thought upon which the Hippocratic work was developed[10-13]. In consequence, the contribution of the natural theory of the putrefied residues of the old Egyptian medicine and of the pre-Socratic philosophy initiated by Thales of Miletus allowed for a naturalistic and rational conception of disease to gradually emerge, i.e., the episteme of medicine. This in turn laid the foundations for an art of healing (*ars medicina*, or *technê iatriké*) based both on the natural causes of disease and observation guided by rational strategies[13,14].

Prior to referring the history of some causal and natural approaches to disease, it is important remembering that philosophical materialism includes naturalism and that its central thesis is that beings are material. In this philosophical context, the existence of immaterial beings is denied, i.e., there are no divinities, spirits, ghosts or ideas independent of a knower subject. On the other hand, realism establishes the independence between our cognitive processes and both the existence of objects and their properties. Note that a variant of the realistic proposal is naturalistic realism. It's important to make some considerations on what the term *natural* designates. According to some authors, something natural is something relative to *nature*, a term that comes from the Greek *physis*, a noun derived from the verb *phyo*, which is translated as *to produce*, *generate*. In consequence, nature might be assumed to be, in general terms, a self-existing category. In this sense, Empedocles used the term *phys* as *birth*. However, in Homer's *The Odyssey* (8th Century B.C.), this word is already used to designate what today is understood as nature, i.e., "a thing's own and constitutive form of being"[15-17].

To formulate the central postulate of materialism, both the concept of matter and reality are necessary since, according to materialism, only material objects are real. When something is said to "be real", the intention is to say that it is objectively real, i.e., that it exists independently of all knower subjects. And when something is said to be subjectively real, the intention is to say that it exists only as part of a subjective experience. However, how can we know if something is objectively real? That will require a general objective reality criterion, a rule that allows deciding if that what is perceived or thought exists independently of human beings. For some thinkers, this criterion indicates basically a relationship with the fact that for something to be real it is enough, although not necessary, that it influences on other object or is influenced by it. Additionally, to define the concept of matter, it is advisable to build upon current scientific knowledge, which differentiates material from inmaterial objects based on the fact that the former change[18,19].

The main natural causal approaches to human disease that have been developed throughout time are exposed next. With the purpose to organize this task, natural causes of disease are distinguished from those that are irrational.

Rational natural causes of disease

Within the naturalistic and rational focus on causal approaches to disease that have been developed throughout the history of mankind, the following should be highlighted: the putrefied residues, the humoral, the atomist, the contagious, the cellular, the molecular and the ecogenetic approaches.

Putrefied residues approach

Ancient Egyptians, in spite of never having proposed the idea of infectious agents, created a theory centered on a noxious substance they named *wechdu* or *whdw*, which resided in the large bowel. This term was used to designate the etiologic agent of different diseases. They proposed that this agent could pass from the gut to the bloodstream, generating its coagulation and pus. They considered that the increase of *wechdu* produced fever and could alter the pulse rate. Given that this substance caused the disease, its cure consisted in getting rid of it by means of different strategies, but they also tried to prevent diseases by means of purgatives, as the Greek historian Herodotus (484-425 B.C.) wrote, since during a visit to Egypt he observed that Egyptians resorted to purgatives three days of each month. In ancient Egypt there was the belief that, although intestinal rotting processes were a constant danger, they were unavoidable, since foods were necessary to maintain life, and they knew that they were subject to breakdown processes that generated putrid substances[20-22]. According to the London Anonymous Papyrus, it is possible that the diffusion of the putrefied residues theory would be owing to the Greek physician Euriphon of Cnidus (5th Century B.C.), author of the *Cnidian sentences*, who substituted the term *whdw* for *peritomata*[21,23,24].

Humoral approach

Medicine would never have come to become a science without the celebrated contribution of the first Ionian philosophers of nature, who pretended to find the key to the world's enygmas through impartial observation and rational knowledge. These thinkers attempted to explain the world without invoking supernatural agents and defined their activity as an "investigation about nature" (*historia peri physeos*)[17,25]. Although in the 2nd century B.C., Egyptian medicine already showed some clues of having overcome the magical conception of disease, it was the Greeks who first created a theoretical system upon which a protoscience was initiated. This process was strongly influenced by the *physis* concept developed by Ionian philosophy[26]. However, it has been pointed out that the explicit separation between medicine and healing processes based on a magical-religious conception was established with the Hippocratic writings[27,28]. Hippocrates of Kos (460-370 B.C.) characterized medicine as a technique and, consequently, the supernatural conception of disease was overcome by a rational conceptualization. Following on Alcmaeon of Croton's thought, the philosopher from Kos understood that disease was a process of unbalance in man's nature. When the natural balance was altered, disease made its appearance. According to Hippocrates, not only were there four types of bodily humors in man (blood, black bile, yellow bile and phglegm), but their unbalance was the cause of diseases.

Subsequently, Galen of Pergamon (129-c. 200 A.D.), based on the Hippocratic theory, developed the concept of dyscrasia. According to this theory, health is a condition of harmony and balance between humors, i.e., a state of eucrasia, and the opposite generated disease. Health was proposed to be maintained as long as there was proportionality of nature's elements, or isomoiria (ισομοιρία, 'equal participation', derived from the adjective ισος, 'equal in number, size, strength, etc.', and from μοιρία, 'part, fee, portion')[29-32]. Therefore, in this context, human body unbalances, characteristic of diseases, were no longer due to the influence of deities or malignant spirits, but to natural factors. It should be noted that, although the Hippocratic vision was physiological, he was not unaware of a comprehensive perspective of human disease, since he gave importance to the environment of the sick individual. Nevertheless, Hippocratic physicians failed to overcome the dichotomy between disease and illness, i.e., between the objective and the subjective components of disease[33].

Atomist approach

Another naturalistic approach to disease, although less influential than the humoral approach, was atomism, which associated disease with an unbalance of atoms. Adequate flow of solid particles was correlated with health, and their stagnation or plethora, with disease and death[34]. Prior to the consolidation of Leucippus (5th century B.C.) and Democritus of Abdera's (460-370 B.C.) atomism, similar ideas already existed, such as the geometric atomism of the Pythagorians

and the "seeds" hypothesis by Anaxagoras of Clazomenae (c. 510-c. 428 B.C.). Anaxagoras proposed the existence of tiny particles that composed things and also pointed out that the different properties of things were dependent on the predominance of one seed or another. The father of atomism was Leucippus, who proposed that things were constituted by countless indivisible particles (atoms) and that the permanent change of the world's aspect was owing to constant readjustment of atoms. Democritus' work allowed atomism further development, which consolidated as a general theory of the world's reality. This theory not only proposed the existence of moving atoms, but that the appearance or secondary qualities of things would be the consequence of both movement and formation and dissolution of atom aggregates. In addition, these corpuscles and the void where they moved were considered indivisible, immutable and imperceptible. In sum, for atomism, atoms and void are the principles of nature, as well as the constituents of the soul[10,35].

An atomist thinker influential on medicine was Erasistratus of Ceos (310-250 B.C.), who thought the body was constituted by atoms. His approach on disease and therapeutics was the one characteristic of mechanistic atomism, according to which vital movements were driven by displacement of material corpuscles inside the body. A force originating in atoms exerted its influence on blood, air and animic pneuma, enabling an adequate nutrition of the bodily organs[36,37]. Other thinkers that incorporated atomist ideas to their medical theories were Aegimius of Ilia (2nd or 4th century B.C.) and Asclepiades of Bithynia (124 or 129-40 B.C.). The latter abandoned the humoral Hippocratic theory and founded the methodist school of medicine based on Heraclides Ponticus' (c. 390-c. 310 B.C.) atomism. Since for Asclepiades disease was the consequence of an alteration of the movements of atoms that constitute the body, it can be stated that the application of atomism to physiology enabled the methodism to formulate a mechanistic vision of medicine, which was popular among physicians up to Galen's epoch[10,38,39]. According to Erasistratus, disease was associated with a state of blood excess, or plethora, a condition that could affect all organs of human body, including the heart. Erasistratus proposed that the vascular system did not only distribute blood, but also what he called *pneuma* (*spiritus* in Latin). He specified that arteries carried the pneuma, and veins only blood. A plethoric status was the consequence of a failure in this process, which entailed an excess of retained blood and the ensuing lack of pneuma in some organ. These theories were directly confronted with those by Galen and the Hippocratic School, which claimed that the circulatory system contained exclusively blood. Galen discredited Erasistratus work, i.e., he criticized that diseases were caused only by an abundance of blood[40,41].

The causal hypothesis of diseases based on humoral dyscrasias and the theory based on atom inbalance exerted an influence that lasted several centuries but, with no doubt, the most infuencial of them was Hippocrates humoral theory, the development and enrichment of which were due mainly to Galen who, by means of his clinical, anatomical and physiological investigations, had a long-lasting influence on European medicine of the Middle Age[42].

Contagion approach

In Hippocratic times, some environmental factors were considered to allow the appearance of diseases. In Arab medicine, the physicians Ibn Khatima (15th century) and Ibn-al Khatib (1313-1374) stood out. With regard to the contagion of a disease, in ancient times, miasma was proposed to be a malignant efflux composed of malodorous and toxic particles, generated by the decay of organic matter. Relationships were established between the miasmata and some febrile states, such as the plague, malaria and yellow fever[43,44]. In the Renaissance, Girolamo Fracastoro (1478-1553) proposed the contagion of diseases. In his work *De contagione et contagiosis morbis*, published in 1546, his studies devoted to the causes, the nature and the consequences of contagion were manifest. He proposed the fundamental seeds of contagion (*seminaria primaria*) without further explaining if they were living or inert matter. However, contagion by living beings (*contagium vivum*) had already been suggested by Lucio Columella (4-c.-70 A.D.) and Marcus Terentius Varro (116-26 B.C.). In spite of his sagacity, Farancastoro had no impact on medicine until the 19th century, when the theory of the existence of microorganisms was scientifically established.

Athanasius Kircher (1602-1680) has been suggested to possibly be one of the first observers that documented the existence of microscopical living creatures[34,45-48], but, with no doubt, it was the work of Louis Pasteur (1822-1895) that allowed for the causal relationship between some diseases and the presence of infectious agents to be established. Indeed, Pasteur refuted the doctrine of spontaneous generation by proposing the germinal theory of infectious diseases. His work was a valuable contribution to the development of immunology, by applying

the anti-rabies vaccine in the first human being, as well as to clinical microbiology, thermal processes for the reduction of infectious agents (pasteurization), etc.[45,49]. Another notable figure was Robert Koch (1843-1910), whose investigations stood out due to the development of microorganism culture, staining and isolation methods. Additionally, in his postulates he proposed several criteria to establish the infectious etiology of some diseases. The work of Pasteur and Koch, and of the representatives of the so-called etiopathogenic mentality, deeply influenced on the advance of scientific medicine[43,45,49-51].

In the mid-19th century, a conception of the human body began to be established and, with new contributions and changes, it remains current to our days. Among the diversity of perspectives of the human body at that time, the following stood up: the cellular vision of the human body, the evolutionist vision and antivitalism and experimental physiology. The latter considers the body as a grouping of cells whose regulations are correlated with physical and chemical processes. In this context, under the notorious influence of Claude Bernard (1813-1878), there was a turn in 19th century medicine: nosology based on the description of anatomical lesions started being replaced by a nosology based on the pathophysiological processes of symptoms[52]. In the 19th century, the naturalistic approach to the human body and disease tended to predominate.

Cellular approach

After the decadence of the humoral theory, different speculative approaches on disease emerged: astrological, alchemical, animist, iatrophysical, etc. Thanks to the work of Rudolf Virchow (1821-1902), the replacement of these approaches with a scientific and rational one was achieved[53]. Virchow had been skeptical with regard to bacteriological and etiologic discoveries associated with diseases, suggesting a multi-causal relationship between man and disease[54]. Virchow's importance lies in that, in view of the speculative chaos that originated after the decadence of the humoral theory, he created a new paradigm in medicine: cytopathology. In *Die Cellularpathologie: In ihrer Begründungm auf physiologische und pathologische Gewebelehre* he described that every cell originates from other pre-existing cell (*omnis cellula e cellula*). Furthermore, he pointed out that cells were the elements of health and disease, and concluded that it wasn't the organism that fell ill, but some cells or groups of cells[53,55,56]. His most important contribution to medicine was the idea that cells were the fundamental units and constituents of all tissues and organs, and that disease occurred when cells were not able to carry out their functions adequatelly. By assuming that cells were the essential components of life, the possibility of explaining disease with humors, animism or other speculations was abolished[57,58]. Consequently, given that since Virchow it wasn't the body what became ill, but some of its cells, cytopathology became especially important. In fact, in the context of Virchow's work, all pathology was claimed to be ultimately cellular. Therefore, diseases could be characterized not only by a group of symptoms, but also by specific tissue changes[59].

Molecular approach (genetic and genomic medicine)

The study of trait inheritance was established by Gregor Mendel (1822-1884), who verified that many of these traits were under the control of two different factors, one originating in the male progenitor, and another in the female sex. Mendel pointed out that these traits were not linked to each other, but were separate hereditary units (currently known as chromosomes), and that a trait could be dominant over the rest. In the early 1900's, with the rediscovery of Mendel's work, Wilhelm Johanssen (1857-1927) introduced the term *gene* to refer to the factors that carried the hereditary traits of an individual[60]. Thanks to the advance of genetic studies, a molecular conception of disease was established, which attempted to explain it in terms relative to genetic processes. According to genetics, some diseases could be explained by knowing the variations in elements of the biochemical and physiological apparatus of cells, i.e., the products of genes: the proteins.

In the beginings of the 20th century, medical diagnosis went gradually focusing specifically on the cell, then on biochemical processes and, finally, on some specific cellular molecular properties. In the past 50 years, genes in particular have been regarded as very important entities in pathogenic processes[61]. With regard to the relationship disease-gene, if a disease correlates only with certain gene, it has been established to be of the Mendelian type. This type of inheritance contemplates dominant or recessive autosomal, X chromosome-linked and Y chromosome-linked diseases. If, on the contrary, a disease is related to several genes, then it is proposed to be of the non-Mendelian type, or polygenic. It should be noted that most polygenic inheritance diseases are, in addition, multi-factorial, i.e., the presence of different environmental factors

is important for their manifestation (gene-environment interaction). Since in multifactorial cause disease genetics is insufficient to explain their occurrence, the concept of genetic predisposition has been proposed. Consequently, the expression of disease would arise from the interaction of predisposing genes with a specific environmental context[62].

From the molecular point of view, genes are a nucleotide sequence of a molecule known as DNA. The DNA contains the genetic code of living organisms, i.e., the necessary information to build other cell components, such as proteins and RNA molecules. Although in 1953 Francis Crick (1916-2004) and James Watson (1928-) announced the DNA double helix structure[63,64], and for this reason they were awarded the Medicine Nobel Prize in 1962, already in 1869, Friedrich Miescher (1844-1895) had managed to isolate what he called nuclein from a pus sample. Not only did he discover that nuclein was present in the chromosomes, but, subsequently, in 1893, he established its advocacy for the theory of chemical inheritance[65]. Thanks to the discovery of the structure of DNA, different human genes were identified and, the development of the full-list of human genes was gradually achieved.

The Human Genome Project (1990-2003), the objectives of which were, among others, to identify the DNA of the approximately 20,500 human genes, determine the sequences of the 3,000 million of base-pairs that compose it and store this information on databases[66], has allowed for human diseases to be considered in a more general form, attempting to elucidate the molecular details of both the cell structure and its phylogeny and ontogeny. In addition to genomics, i.e., the study of full genomes, there are several related fields, such as pharmacogenomics, nutrigenomics, metabolomics, proteinomics, toxicogenomics, etc.[67].

The study of the human genome has not only enabled the sequencing of the base pairs that comprise the DNA, but also the discovery of a large number of common genetic variants. Although there is great similarity among human genomes, close to 99.9%, the rest constitutes the genetic, endophenotypical and phenotypical variants between individuals. The variability of the human genome and of that in other species has been associated with single nucleotide polymorphisms (SNP). Athough the nucleotide sequence of the human genome is very much alike between different individuals, there are positions where a nucleotide differs from an individual to another. Currently, more than 10 million SNPs have been described, although it has been proposed that there would be approximately 20 million[68]. Many SNPs are known to have no effect on the cell function, but others might influence on the predisposition to suffer diseases in response to infectious agents, toxins and drugs.

With regard to the applications of genetics and genomics to medicine, genetic medicine has been established as a discipline that deals with the application of genetic principles to medicine practice and genomic medicine refers to the use of large scale genomic information, i.e., it considers the genome, proteome, transcriptome, metabolome and/or epigenome characteristics of an individual in the practice of medicine[69]. In summary, the difference between genetics and genomics lies in that in the former, specific genes are studied, while the latter looks into the functions and interactions of all genes in a genome[62]. It is important to point out that, although the genome possesses all the information necessary to codify and express all proteins of an organism, only a fraction of the protein repertoire is expressed in a determinate type of cell, i.e., although all cells of multicellular organisms have the same genetic information, different genic expression programs are generated in some types of somatic cells. This is due to different epigenetic mechanisms such as, for example, DNA methylation[70]. Therefore, the epigenome plays a fundamental role in the control of gene expression. On this regard, it should be mentioned that, although the epigenome programation is established during embryonic development, it can sustain modifications throughout an individual's life in response to different environmental factors such as diet, consumption of substances (including drugs) and social interactions[71]. From the dynamism of epigenetic regulation has emerged what has been termed as phenotypical plasticity, which is a relevant property for the adaptive and pathological development of living beings. The presence of some phenotypical plasticity defects, i.e., some alteration in the capacity of cells to change in response to internal or external signals, might correlate with a pathological state. Consequently, better knowledge of the epigenetic mechanisms of a disease would not only enable assessing the risk to develop it, but also the design of specific therapeutic strategies[69,72]. In summary, epigenetics is typically defined as the study of inheritable changes in gene expression that are not due to changes in the DNA sequence. Epigenetic changes are crucial to the development and differentiation of the different types of cells in an organism, as well as for normal cell processes. However, epigenetic states can be disturbed by environmental influences, generating different diseases[73].

Ecogenetic approach

When considering the interactions between the genome, the epigenome and the environment, an ecogenetic perspective of diseases has been developed. The debate on the importance of inheritance in comparison with the environment in the origin of diseases has been going on for more than a century. In fact, the expression "nature versus environment" was coined by Francis Galton (1822-1911) to distinguish between the characteristics one is born with and those acquired from the surroundings[74]. However, the history of ecogenetics usually goes back to the beginnings of the 20th century, when Archibald Garrod (1857-1936) elucidated the role of inheritable metabolic variants in some rare genetic diseases, which he named metabolism innate errors. Even when he did not use the term *gene*, Garrod proposed both the concept of chemical individuality and the importance of genetic factors in the development of diseases[75].

Later, in the decade of 1950, some drug adverse reactions were shown to occur in individuals with a specific enzymatic variant. This laid the foundations for the emergence of pharmacogenetics, i.e., for the study of genetic variations in response to drugs. Based on different discoveries, it has been possible to establish that the effects resulting from exposure to exogenous substances or xenobiotics not only depend on their intrinsic properties, but also on variations in the sites of their action, as well as on variants on biotransformation enzymes and other factors of the host. The extrapolation of the notion that genetic variations affect the responses to any type of environmental agent and not only to substances, led to the development of ecogenetics. In this context, the proposal of genetic susceptibility, in contrast with specific diseases associated with determinate genes, is neither necessary nor sufficient to cause a disease, but it modifies the risk for developing it in a specific environmental context[76]. In 1971, George Brewer coined the term *ecogenetics* to broaden the concept of genetic variation beyond drugs, xenobiotics (chemical substances) and other environmental agents[75-78]. Ecogenetics studies the importance of genetic polymorphisms in organisms' response variations to different environmental factors. The result of such variability is a genetic vulnerability against a determinate environmental factor. According to the ecogenetic perspective, diseases are due to the interaction of genetic vulnerability with the environment. For this reason, depending on the environmental agents involved, we can talk about infectious ecogenetics, nutritional ecogenetics, chemical ecogenetics (including pharmacogenetics), etc.[78].

Consequently, in this context, the discussion on the predominance of genetics over environment, or vice versa, is futile because, in general, neither the genes, nor the environment by themselves are determinant to the development of a disease. Therefore, the understanding of the risks for the development of diseases, as well as the prediction of the therapeutic and adverse effects of drugs require for the gene-environment interactions to be considered[75]. The initiation of the Environmental Genome Project (EGP) has represented the first large-scale effort to discover the susceptibility of alleles that might be important in the gene-gene or gene-environment interactions[74].

Irrational, esoteric and mystical natural causes of disease

Considering the use that will be made of the epithets *irrational*, *esoteric* and *mystical*, it is necessary to refer to each one of them. Athough there is no consensus on the meaning of the terms *rational* and *rationality*, before referring to what the term *irrational* designates, it is convenient to know, in broad terms, what by *rational* is t be understood. Reason is usually defined as a cognitive faculty that enables a judgment that is adequate, coherent and consistent with reality, in addition to the inferences established for this purpose. Rationality has been pointed out as being associated both with the formation of beliefs and with cognitive processes to make decisions. In consequence, strictly speaking, a belief cannot be determined as being rational without knowing the underlying cognitive decision processes, i.e., in order to determine the rationality of a decision, its formal consistency has to be measured. Therefore, an individual can be rational (partially) in spite of having false beliefs provided that, in some sense, they are consistent[79-81].

From the perspective of the contents of our knowledge, i.e., of our beliefs, it could be proposed that, under empirical and rational ascertainment criteria, a belief can be qualified as irrational or partially rational if it doesn't fully adjust to reality. Exposed in a simple way, irrationalism is present in those doctrines that underestimate or deny the power of reason and propose replacing it with religious illumination (mysticism), feeling (emotivism), intuition (intuitionism), will (voluntarism), action (pragmatism), pure experience (radical empirism) or any other approach. Therefore, the irrationalist does not seek rational (global) reasoning, but

tends to affirm or deny under cognitively arbitrary assumptions[1,6,82]. To support a claim, an individual may have rationally elaborated thoughts and acts (logically developed and in an organized way), but conceptually supernatural, magical or fantastic (unreal beliefs).

The term *esoteric* comes from the Greek word εσωτεριχος, which refers to 'that belonging to what's inside', and from the word εσωτερω (*esoteros*) that means 'interior' and that in some senses is used as occult, secret or misterious. The origin of these terms is found in the word εσω (*eso-*), which means 'inside', and hence it tends to be used to refer to secret or occultist doctrines, whose knowledge is typical of chosen ones, wisemen, fortune-tellers and prophets[83,84]. The term *esoterism* is often used as an attitude towards knowledge that entails the distinction between vulgar, popular and superficial knowledge and authentic and unique knowledge that is reserved for the chosen one, the wise and the prophet[85]. Finally, the term *mystical* comes from the Latin word *mysticus*, which means 'of secret rites', and from the Greek *mystikos*, 'secret, connected with mysteries'[2].

Although during the Renassaince medieval oscurantism was overcome, and there was remarkable development on science and medicine, superstition and occultism did also develop. For example, medicine was strongly influenced by astrology, alchemy and other varieties of mysticism[86].

In the history of causal approaches of the irrational, esoteric and mystical types towards disease, the following can be highlighted: the astrological, the alchemical, the iatrochemical and the iatromechanical approaches. Next, these approaches are reviewed, as well as others with less historical impact.

Astrological approach

Astrology is the belief in the influence of the movements of the stars on the destiny of men. In the beginnings of the use of this term in ancient Greece, it simply meant hat we currently understand as astronomy[5]. There was also the term *astromenteia*, which referred to the art to predict the future by observing the stars[25]. The relationship between disease and astrology was notorious between late Middle Age and early Renaissance. In this period, the belief on the influence celestial bodies exerted on different human activities was relevant. With regard to medicine, many physicians on that times claimed that diseases and health were influenced by the position of the stars. In fact, during part of the middle Ages man was conceived as a microcosm that reflected the Ptolomean macrocosm; therefore, the body parts were influenced by Zodiac signs. This conception was depicted in the *Zodiac Man*, a work where human body parts are represented in correlation with the 12 Zodiac signs.

Later, in the Renaissance, the first medicine book containing different anatomical illustrations was published, the *Fasciculus medicinae* (1491), which presents, among its illustrations, that of the Zodiac Man[87]. Medical astrology occupied a prominent place in the Renaissance, and has been considered for some as a continuity of popular medieval doctrines that were not linked to academic medical theories. In spite of the fact that many Renassaince medical treatises explicitly condemned astrology, many European physicians resorted to horoscopes to determine the opportune time to perform some therapeutic interventions[86,88]. In this period, Teophrastus Bombast von Hohenheim (1493-1541), known as Paracelsus, stood up; for him, cosmic order and astrology were relevant, as he established in the *Astrum in corpore* doctrine, where he described man as a microcosmos. Similar to speculations of some pre-Socratic, Platonic and Middle Age thinkers, Paracelsus developed an analogy between the micro- and the macrocosm[89,90]. Paracelsus' theories had religious influences (medieval, Lutheran and other spritualist trends that were dissident for his epoch), in addition to influences of neo-Platonism, Hermetism and the gnostic elements of Renassaince philosophy. In general, the Paracelsian work is said to have been affiliated both to the religious culture of his time and the philosophical and scientiic currents of Renassaince[91].

With regard to Lutheran influences, it has been pointed out that Paracelsus went further tan Martin Luther (1483-1546), since he developed a medical philosophy that acknowledged the divine power manifestations with regard to the arcane forces of nature[91]. As for the development of his ideas, it is assumed that in his beginnings, around 1520, his perspective was rather naturalistic; however, between 1524 and 1525, influenced by his religious studies in Salzburg, his naturalism had a strong religious component. The peculiarity if his work lies in that his writings present a type of speculation that is more characteristic of mystical contemplation than of empirical evidence[92,93]. In *Paramirum* he postulated the doctrine of the five spheres, which determined health and disease. The five spheres, or *entia*, that determined human life were the following: *ens astrale*, *ens veneni*, *ens naturale*, *ens sprituale* and *ens Dei*. *Ens astrale* stands for the realtionship that every person who is born has with a constelation. *Ers*

veneni refers that man is part of nature and is exposed to suffer the action of the surrounding world. *Ens naturale* alludes to the path man travels from birth to death and is determined by his constitution and destiny. *Ens spirituale* indicates that man has body and spirit. Disease would originate by disturbance of these four spheres' order, but the fifth, *ens Dei*, would participate in its healing[94,95]. Pracelsus not only fought the humoral Hippocratic-Galenic approaches, but, in adition, he individualized disease, stressing on specific external causes[91]. Based on the notion that the body functioned under the influence of an internal alchemy, he laid the foundations of iatrochemical thought, which, together with iatrophysical and iatromechanical thought, had a profound influence on the 17th and early 18th century. One of the physicians who was strongly influenced by Paracelsus was Jean Baptiste van Helmont (1580-1644)[96-99].

Alchemical approach

Alchemy has existed in cultures as the Chinese, Indian, Islamic and Western since the Hellenistic epoch. The word *alchemy* appeared in the Islamic culture, from where it passed to Latin, and is associated with the Greek terms *chemèia* ('art of metal fusion') and *chymos* ('juice')[100]. The most ancient backgrounds known of alchemy are related to its practice in China, in the 4th century B.C. The main purpose of alchemy is usually assumed to be the transformation of metals into gold, but alchemy is a term that encompasses a wide range of doctrines and practices. In Chinese medicine, for example, alchemy comprised the search for health, longevity and immortality elixirs[86]. Both commercial routes and military conquests entailed its diffusion throughout the Hellenistic world. After the Islamic Arabs conquered Alexandria, the learning center shifted to Damascus and Baghdad, where the development of alchemy continued. Alchemical texts were translated from Greek into Arab in the 8th century A.D.; some translations, together with the authorship of other alchemical manuscripts, have been proposed to be the work of Jabir Ibn Hayyan (c. 721-815), whose Latinized name was Geber. Among Arab alchemists, Avicenna (980-1037) and Abu Bakr al-Razi or Rhazes (c. 854-925) also stood up. The influence of Arab alchemists gradually penetrated the Western world where, during the 13th century, some of the most eminent alchemists fluorished[101,102]. With regard to the translation of Greek and Arab texts into Latin, an Italian 13th century alchemist stood up, Paul of Taranto, known as Pseudo Geber, whose influence on medieval European alchemy was highly important[103]. Although in the 17th century a process was started to margin alchemy, both Robert Boyle (1627-1691) and Isaac Newton (1643-1727) devoted part of their efforts to its study. Johann Joachim Becher (1635-1682) is often considered an alchemist and iatrochemist whose writings would have inspired the development of modern chemical theories[104]. Since in Paracelsus work the idea is found that the purpose of alchemy was not only the transmutation of metals into gold, but also the preparation of medications, this author has been considered the founder of the iatrochemical school[105]. In fact, 17th century Paracelsians developed a therapeutics based on the development of chemical or spagyric drugs from plants by means of alchemical procedures[86]. Within medicine, alchemy was more related to healing procedures than with causal speculations about diseases.

Iatrochemical approach

The founder of this medicine general theory was Paracelsus, for whom sensory experience was fundamental; for this reason, he rejected Galenic humors, which were unobservable and considered by him mere speculation. Paracelsus and Van Helmont were the precursors of the iatrochemical doctrine[97-99]. Van Helmont pointed out that the study of nature corresponded to naturalists, and not to priests, and advocated for Paracelsus and magic. These ideas meant that, in 1623, he had to appear before the Holy Inquisition and be condemned to 3 years in prison. He inherited his manuscripts to his son, who published them in 1648 as *Ortos medicinae*. For van Helmont, disease was related to the *Archeus* or vital principle of the entire organism, a gas both spiritual and material that generated the *Ens morbi* from an abnormal seed. Once generated, this seed became independent from the *Archeus*, following its own course, being able to even destroy the *Archeus*. Therefore, external agents were unable to directly produce a disease, but were able to cause it through the *Archei*. Another important iatrochemical physician of the 17th century was Thomas Willis (1622-1675), who also was animist. Willis postulated the existence of five elements and adopted the ideas of fermentation previously proposed by Franciscus Sylvius (1614-1672), also known as Franz de le Boë. He claimed that diseases were caused by fermentations and effervescences, where vital spirits played a main role. Later, in the mid-18th century, the iatrochemical school started losing prestige due, on

one hand, to the emergence of iatromechanical currents and animism, and on the other, to the influence of Thomas Sydenham (1624-1689) and Herman Boerhaave (1668-1738), who proposed a less speculative, more clinically focused medicine[97,106].

Iatromechanical approach

During the 18th century, mainly thanks to Franciscus Sylvius, iatromechanics came to the foreground[97]. This doctrine was constructed based on an analogy between the human body and a machine, and attempted to explain the functioning of the former on purely physical bases. It stated that the solid parts of our body constituted different pieces of machinery governed by the laws of statics and that bodily fluids functioned under the principles of hydraulics. While iatrochemistry stressed on qualitative aspects of medicine, iatromechanics emphasized on the quantitative analysis of diseases. The combination of a solidistic stoichiology and a conception of physiological activity founded on movement (forces) of organic parts was the basis of iatromechanics or iatrophysics, which, together with the iatrochemical approach, was current during the 17th century and part of the 18th [98,106].

In his *Traité de l'homme et de la formation du foetus*, published in 1675, René Descartes (1596-1650) considered the human body as a material machine governed by a rational soul, located in the pineal gland. His work was perhaps the first attempt to contain the entire animal physiology in a mechanistic theory. On the other hand, the work *De motu animalium*, by Giovanni Alfonso Borelli (1608-1679), is considered the first complete treatise on biomechanics. In fact, Borelli analyzed the function of the locomotor system in man and other living beings from the mechanical point of view[99,107]. Among the iatromechanics physicians, Santorio Santorio (1561-1636), who also was one of the first ones to introduce quantitative methods in medicine, and Giorgio Baglivi (1668-1706), who established the difference between theory and practice of medicine, also stood up[98,99,106]. It should be noted that a system very close to iatromechanics was the so-called mechanic-dynamic approach, proposed by Fiedrich Hoffman (1660-1742), for whom both life and death depended only on physical and mechanical causes. Hoffman's system was based on anatomy and physics, and its central element was movement. His approach was based on heart movement and blood circulation, discovered in the early 17th century. However, since this theory wasn't enough to explain the consequences of infections, Hoffman postulated the existence of a qualitative principle, a subtle and spirituous fluid, only perceptible by its effects. As he considered this principle to be the cause of vital activity, he drifted away from his initial premises and became a precursor of animism[98,106].

Other approaches: irritability theory, solidism, brownism and mesmerism

During the Baroque, many medical speculations emerged trying to substitute the humoral theory, such as the irritability theory, solidism, brownism and mesmerism.

Francis Glisson (1597-1677) introduced the term *irritability*, but the theory was due to Albrect von Haller (1708-1777), who developed this concept more widely, based on numerous experimental data. Von Haller looked for a theoretical alternative to the conflict between iatrochemists, iatrophysicists, animists and others.

Solidism, or neural pathology, was one of the more intense reactions against the humoral theory. For its author, William Cullen (1712-1790), the nervous system played a central role in human pathology. He proposed that what made people sick were not humors, but solid organs of the body. He postulated the existence of a force or indefinite principle, generated by the nervous system, which started and maintained all physiological and pathological processes of the body. He named this principle nervous force, nervous activity, animal force or cerebral energy.

John Brown (1735-1788) devised a medical approach known as brownism, the fundamental principle of which was excitability, a basic property of living matter that allowed both perceiving and responding to the surroundings. For Brown, this property was not only distinctive between living and dead things; he added that a healthy status was the result of a balance between external stimuli and excitability. Consequently, the physician had to repair unbalances and help to maintain equilibrium. According to Brown, excitability lied in the nervous system; therefore, bodily states would be explained by the relationship between excitability and emotions. He stated that deficient stimulation was bad, but if it was excessive, it could be worse, since it would eventually lead to a state of weakness by excitability exhaustion. Although he was Cullen's disciple, Brown questioned some aspects of his teacher's theory, and concluded that there were two types of general diseases: those resulting from excessive excitability (sthenia) and those resulting from deficient excitability (asthenia)[108-113].

Finally, mesmerism was introduced by Franz Anton Mesmer (1734-1815). In 1799 appeared his book *Mémoire sur la découverte du magnétisme animal*, where he summarized his ideas. Although during the Age of Enlightement reason was privileged, magic and mesmerism were also practiced. Mesmerism was rejected by official scientific circles and, in 1783, an investigating commission declared that Mesmer was a charlatan. In spite of this, there were many followers of mesmerism, especially among those who had affinity for the supernatural, esoteric and mysterious as, for example, *Naturphilosophie* adepts. Mesmer theorized on the existence of natural energy transference between animated and inanimated objects. He named this approach animal magnetisn, and later it became known as mesmerism. Since some physicians and scientists of that time considered mesmerism to be quackery, James Braid (1795-1860) coined the term *hipnotism*, in an attempt to separate mesmerism from both spiritism and charlatanism. James Esdaile's (1808-1859) interest for mesmerism was such that he used it as anesthetic in his surgical interventions. Finally, hipnotism turned out to be more important for the development of psychoanalisis than for surgical anesthesia. As a matter of fact, Sigmund Freud's (1856-1939) professor, Jean Martin Charcot (1825-1893), and Josef Brauer (1842-1925) used hipnotism on their studies on hysteria[114-118].

Conclusions

When the history of human questionings on the causes of disease is reviewed, it can be confirmed that this uncertainty has aroused permanent concern, curiosity and explicative attempts. Consequently, a wide range of causal proposals has been developed, with the naturalistic approaches standing out, since they are the source of medical scientific activity and medicine philosophy current debates. However, it is important to note that a naturalistic causal approach does not necessarily include an entirely rational posture. If by rational is to be understood what was described in previous paragraphs, all naturalistic causal approaches, except for those developed under the scientific method, are relatively irrational. Within the range of causal approaches here exposed, some are clearly more rational than others. The main purpose of this monograph has been to provide the reader a historical review of some of the causes of disease distinguishing between ontological and gnoseological concepts, i.e., between the existential category of (natural) causes and their relatively rational or irrational characteristics, respectively.

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