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The Holistic Approach of Evolutionary Medicine: An Epistemological Analysis

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THE HOLISTIC APPROACH OF EVOLUTIONARY MEDICINE: AN EPISTEMOLOGICAL ANALYSIS

Evolutionary medicine is a new discipline characterized by a holistic approach to health and disease based on the theories and concepts of evolutionary biology. Unlike many previous medical holisms, evolutionary medicine seems to integrate medical and biological specialities without pretending to be an alternative view to 'orthodox science.' The holism of this approach, in fact, is based on a unifying rational principle – natural selection – that can produce hypotheses and previsions which are experimentally testable. In this text, I investigate aspects of the human body and mind, as well as the principles and the methods through which evolutionary medicine found a holistic perspective of health and disease. The aim is to underline the epistemological structure of this approach, shaping a context for further discussions about its nature, legitimacy and applicability.

Introduction

Evolutionary or Darwinian medicine is a new discipline, born in the 1990s, and its aim is to apply evolutionary thinking for a better understanding of problems in clinical medicine, pathology, epidemiology and public health (Williams and Nesse, 1991).

> Evolutionary medicine [...] is a growing and central discipline that applies evolutionary knowledge to the understanding of human biology, both normal and abnormal. It is an essential science, necessary for a holistic perception of how health and disease emerge (Gluckman et al., 2010, p. XV).

This significant passage appears in the last monograph published in the field: *Principles of Evolutionary Medicine* by Peter Gluckman, Alan Beedle and Mark Hanson.

Holism is a concept which, generically, concerns that the properties of any complex entity are determined not by its components alone, but by the whole of its parts, this whole being something *more* than a simple sum of the parts. More precisely, it means that a given domain of reality, or reality itself, is originated from one *element*, or governed by a uniform *principle*, which is undetectable with analytic and separate studies of the parts which compound the domain. Holism is the Platonic affirmation that reality came from the 'One.' But holism could also amount to saying that life is based on DNA, or that matter is based on quarks and leptons, because these are natural elements considered as the base of complex phenomena that they define. Holism can also amount to affirming that life is governed by the two fundamental principles of evolution, natural selection and drift, or that matter is governed by the four fundamental forces: gravity, electromagnetism, weak interaction and strong interaction. Holism in this sense is, above all, a characteristic of *reality itself* and any holistic description is determined by the fact that the object described has a holistic nature. Holism does not mean that the element or principle, supposed to be at the base of the domain studied, is the one and only existing element, but it means that it is the first and most fundamental without which the domain itself would lose its identity and essential features. So, to say that DNA is the fundamental element of life does not mean that it forms life in its integrity, but it means that without DNA, or, at least, without a strictly equivalent surrogate, life could not subsist as such.

Holism has been interpreted as a *method* to *organize* in an integrated whole different forms of knowledge already acquired, or as a *method* to gain *new* knowledge about a given system. In

the first methodological sense, holism corresponds to the process which correlates data from different disciplines with a unifying principle or law. In the second methodological sense, a holistic approach permits to prove that the correlation between data, from different phenomena, is given by the existence of a common *element* or *principle*, between these phenomena, that establishes the correlation. Holism in medicine could be schematically defined, notwithstanding a lot of different historical forms, as the attempt to understand health and disease as properties and emanations of the whole individual, rather than of a single part of his body or mind. Normally, any holistic approach in life sciences views the individual as a system in which body and mind are closely integrated. This body-mind system, moreover, is generally considered as the product of the interplay between heredity, acquired characteristics, development and environment. To be holistic, in this sense, means to believe that to understand humans in their health and disease we cannot treat separately any of the factors just listed.

All types of holistic medicine have been defined in contrast with so-called reductionist approaches

> […] represented as a form of etiological thinking that identifies disease with a single cause, such as a bacterium or a biochemical abnormality. […] It could also signify excessive attention to anatomical localization of disease in specific organs or tissues (Lawrence and Weisz, 1998, p. 2).

Randolph Nesse, founder of the discipline of holistic medicine with George Williams (1926–2010) in 1991, often referred to holistic concepts, even without using this specific term, in order to describe the epistemological function of evolutionary medicine. In 2005, for instance, he wrote:

> The greatest value of an evolutionary approach is not some specific finding or new therapy, but it is instead the framework it provides for uniting all aspects of a biopsychosocial model (2005, p. 903).

Evolutionary medicine displays typical aspects of a holistic approach. It is a holistic science because it studies a holistic phenomenon. Evolutionary processes that involve all the aspects of individuality, in fact, determine health and disease: physical, developmental, behavioural and psychological. This does not mean that every individual disease, every time, is determined by the same factors, but it means, at least, that our understanding becomes deeper as more factors about individuality can be related to pathological phenomena.

Evolutionary medicine is holistic also in a methodological sense. From one perspective, as seen in Nesse's quotation, evolutionary medicine claims that it could be the framework needed in order to integrate the different disciplines that study human health and disease. From another, evolutionary medicine offers a *new* type of knowledge about health and disease. To see the body as a product of evolution offers a new perception undetectable by traditional mechanistic approaches (Nesse and Williams, 1994, pp. 6–7). The problem of holism in medicine emerged in a precise historical period. During the interwar years of the twentieth century many physicians, intellectuals and politicians, tried '[…] to resist what they saw as reductionism and excessive reliance on technology' (Lawrence and Weisz, 1998, p. 1). In this context, South African philosopher Jan Christiaan Smuts (1870–1950) coined the term in his *Holism and Evolution* (1926). In this famous text, Smuts tried to show that the theory of evolution provided unity between phenomena previously considered separated: matter, life and mind:

> This factor, called Holism in the sequel [later in the book], underlies the synthetic tendency in the universe. This is the principle which makes for the origin and progress of wholes in the universe. An attempt is made to show that this whole-making or holistic tendency is fundamental in nature and that it has a well-marked ascertainable character. Also, that Evolution is nothing but the gradual development and stratification of progressive series of wholes, stretching from the inorganic beginnings to the highest levels of spiritual creation (1926, p. iii).

The holistic movement in the interwar period was complex. In medicine this movement was characterized sometimes as the attempt to integrate reductionistic laboratory sciences, sometimes as a new way to improve the quality of human relations in clinical medicine, sometimes as an alternative medicine like homoeopathy. Holism has been interpreted sometimes as the approach to understand the individuality of patients; at other times as the approach to understand individuals through concepts of type, race or nationality.

However, despite this specific historical context, we can also admit the existence of holistic approaches long before this period in which the term has been coined. Lawrence and Weisz, in their monograph on the topic, refer for instance to a holism characterized by any

> [...] integrative and comprehensive intellectual approaches to phenomena. Perspectives of this type have existed since antiquity and undoubtedly constitute a permanent tendency in western intellectual life (1998, p. 6).

This paper, given that we are focused on the holistic approach of evolutionary medicine, deals with a form of holism characterized not by a rejection of science and scientific medicine, as has frequently been the case with holism of the interwar period, but, on the contrary, by a genuine scientific attempt to understand the human body, at the point that we could define this type as 'scientific holism.' We are aware that the distinction between 'scientific medical holism' and 'not-scientific' or 'alternative medical holism' could be simplistic. It involves the problem that the meaning of 'science' changes dramatically over time and that some holistic systems may straddle science and alternative approaches. However, this distinction seems functional as a means of characterizing holism as developed in evolutionary medicine. Charles Rosenberg gives, in a paper on 'Holism in twentieth-century medicine,' four different meanings of medical holism (Rosenberg, 1998). 'Historical holism' views the body in its evolutionary history. 'Organismic holism' views the body as a functioning unit taking arguments from vitalism and the concept of 'design.' 'Ecological holism' studies the body in particular social and physical settings and is founded upon the approaches of social medicine. Finally, 'worldview holism' is more focused on society as a unified whole.

Now, the holistic approach of evolutionary medicine is clearly referable to the first type of holism. Rosenberg, in fact, quotes Paul Ewald who has been a pioneer in evolutionary medicine and one of the most active scientists in this field (Rosenberg, 1998, p. 338, note 8). Moreover, he states that:

> Most such efforts to place health and disease in the context of evolution were not meant as categorical rejection of mechanism—in some cases quite the contrary—but an effort to place those mechanisms in a larger integrative framework (1998, p. 338).

Nonetheless, Rosenberg referred to an early application of evolutionary biology to medicine which emerged from the 1900s to the 1940s. By contrast, it is fundamental to note that the 'integrative framework' in which *actual* evolutionary medicine places health and disease came from a more sophisticated evolutionary biology which seems much more 'scientific' than evolutionary biology of the first half of the twentieth century. In fact, in that period, the discipline was not yet considered a 'hardcore science' as it is now. The 'new' evolutionary biology is based on molecular biology and on mathematical models of how natural selection works.

Actual evolutionary medicine, by consequence, is more complex than those previous attempts. Its holism can be categorized also as 'organismic' and 'ecological.' Thanks to this new evolutionary biology, evolutionary medicine uses arguments from the concept of 'design,' but without referring to transcendental properties of matter. Thanks to the models of social interactions recently developed, it can also apply evolutionary concepts to human behaviour and society. The fact that evolutionary medicine can apply holism in all these different domains (history, organism

and society) with the scientific approach of evolutionary biology, is, we believe, the most striking characteristic of this approach. This is scientific approach which does not deny mechanism and reductionism, and hence does not deny science, but which locates itself, at the same time, in a wider perspective, because it tries to integrate different domains and phenomena.

Evolutionary Biology and Holism in the Second Half of the Twentieth Century

To see the body as a product of evolution often implies the use of a holistic perspective. The first book in which the term 'holism' appeared has been *Holism and Evolution* (Smuts, 1926), where the evolutionary perspective was used to analyze in an integrated whole the different aspects of human nature – matter, body and mind – previously considered separated.

Now, in any case, we are dealing with a different and more refined evolutionary biology that is the product of several advances realized in the second half of the twentieth century. Only this new evolutionary biology, in our opinion, disposes of the necessary conceptual instruments to found a scientific holistic perspective. Stephen Stearns, introducing evolutionary thinking in the first chapter of his *Evolution in Health and Disease*, wrote that:

> Evolutionary biologists want to understand how the variation in reproductive success that causes selection arises, how the genetic variation that enables a response to selection originates and is maintained, and how that response is constrained by geography, time, inheritance, conflicts, development, and history (1999, p. 3).

The focus of evolutionary biology is on genes variation and selection, but this implies a wider view that concerns many relationships such as those between genes, development, individuals, populations, history and environment. Gluckman and collaborators, in their *Principle of Evolutionary Medicine*, give an even more holistic definition of evolutionary theory focused on the concept of 'design':

> Evolutionary biology is fundamentally concerned with the various processes that have determined the 'design' of the human body at all levels, from how we interact as whole organisms with other members of our species to every component and level of our internal biology. Design is a term used frequently in the evolutionary literature. It is a metaphor, used as shorthand to describe the various processes by which a species evolves such that its characteristics – anatomical, physiological, biochemical, maturational, and behavioural – fit the environment in which the population lives (Gluckman et al., 2010, p. 8).

The second half of the twentieth century is surely marked by the discovery of the 'double helix' which dramatically improved our understanding of heredity and gave a spectacular confirmation to some Darwinian concepts, first of all that of natural selection working on the gradual accumulation of light spontaneous genetic mutations.

From the 1960s, evolutionary biology started to be applied with success also in the understanding of animal behaviour and human emotions. The first step was the theory developed in *The Genetical Evolution of Social Behaviour* published by William Hamilton (1936–2000) in 1964. In this paper, for the first time a mathematical model was proposed able to explain how a detrimental characteristic for an individual as the altruistic behaviour could be positively selected because of its benefit for the genetic pool of the population (Hamilton, 1964, 1964a). Hamilton's theory is founded on the general principle that genes have effects not only in the individuals who carry them, but also in individuals' relatives. This implies that society, reciprocity and social behaviour are essential components of evolution and selection of social animals. As written by Hamilton:

> [...] the theory points out that for a gene to receive positive selection it is not necessarily enough that it should increase the fitness of its bearer above the average if this tends to be done at the heavy expense of related individuals, because relatives, on account of their common ancestry, tend to carry replicas of the same gene; and conversely that a gene may receive positive selection even though disadvantageous to its bearers if it causes them to confer sufficiently large advantages on relatives (1964a, p. 17).

Another development of Hamilton's theory came with *The Evolution of Reciprocal Altruism* published by Robert Trivers in 1971. If the model of Hamilton was restricted to individuals genetically related, Trivers tried to develop a model which could justify the evolution of reciprocal altruism in all individuals of a society, even between those without kinship. This model can be applied to a wide spectrum of emotions related to altruistic and egoistic behaviours:

> Specifically, friendship, dislike, moralistic aggression, gratitude, sympathy, trust, suspicion, trustworthiness, aspects of guilt, and some forms of dishonesty and hypocrisy can be explained as important adaptations to regulate the altruistic system. Each individual human is seen as possessing altruistic and cheating tendencies, the expression of which is sensitive to developmental variables that were selected to set the tendencies at a balance appropriate to the local social and ecological environment (Trivers, 1971, p. 35).

The publication of the famous *Sociobiology* by Edward Wilson represents the crucial turning point for the evolutionary explanation of animal behaviour, even if the part related to humans has been the most controversial (Wilson, 1975). As reported by Michael McGuire and Alfonso Troisi in their *Darwinian Psychiatry*:

> Wilson chose to discuss possible evolutionary origins of human social organizations, barter and reciprocation, bonding, role playing, communication, culture, ritual, and religion. With this discussion, biology intruded itself into the intellectual territories of psychology, sociology, history, law, and moral philosophy, disciplines that had developed their views of human nature largely without recourse to the findings and reasoning of biology. A decade and a half of controversy followed (1998, pp. 35–6).

The criticisms have been focused on the idea, more or less implicit in Wilson's theories, that genes play the ultimate role in human behaviour. The debate has favoured the development of more holistic theories that widely explored the relationship between 'nature and nurture' (see, for instance, Wilson, 1978).

More recently, evolutionary biology increased a new research area, the so-called evolutionary developmental biology (shortened to *EvoDevo*). Biologists have refined the idea that organisms, in their development through life, could carry on different strategies according to the needs imposed by environmental changes and pressures. As defined by Gluckman et al:

> Development is not simply a matter of a fertilized ovum growing and dividing according to a pre-programmed mechanism. There are complex pathways of differentiation from a single cell into an adult human and there are distinct components to the life course: from pre-implantation embryo, to implanted embryo, to foetus, to neonate, to dependent infant, to juvenile, adolescent, and adult. In recent years, major progress has been made in integrating our understanding of developmental plasticity – a set of processes which have themselves evolved – with the remainder of evolutionary thought (2010, p. 42).

The 'discovery' of the importance of developmental processes and plasticity has improved the holistic approach in evolutionary biology, because this aspect, particularly related to life history and experience, has been fully integrated with many others to define human individuality.

Evolutionary Medicine and Holism: 1991–2011

To see the body as a product of this complex whole of evolutionary factors has been the determinant for the birth of evolutionary medicine. The design of the body, precisely because it is the product of different evolutionary mechanisms and principles, is full of compromises and trade-offs. Human diseases are often related to imperfections that are evolutionary determined. As Randolph Nesse wrote in 2001:

> The application of Evolutionary Biology to medicine, known as evolutionary or Darwinian medicine, uses an evolutionary perspective to understand why the body is not better designed and why, therefore, diseases exist at all (p. 358).

Constraints of development, for instance, could determine fundamental compromises in the evolution of a new trait. One of the most popular examples is the evolution of upright posture in humans, which has determined a price in back problems (Williams and Nesse, 1991, p. 17). Given that our body could not be completely redesigned for upright posture during our evolution, we have maintained the basic bodily structure of a quadruped, just slightly modifying some structures as the neck and the pelvis. At the same time, the pelvis in women has become too narrow for a safe birth, a fact at the base of most of the obstetrical problems of our species. Moreover, our viscera are enveloped in a tissue still designed for quadrupeds (the peritoneum); while in the upright posture the viscera, so to speak, hang from a post, a fact which can cause digestive block, haemorrhoids and inguinal hernia (Nesse and Williams, 1994, p. 162). To understand the vulnerabilities related to upright posture we have to take into account almost all the anatomy of the body as well as its development from embryonic life. The evolutionary study of upright posture, moreover, involves adaptationist hypotheses related to the evolution of first hominids as well as more recent social human habits. A rigid upright posture, for instance, during the early nineteenth century, was considered a sign of distinction of civilized elites against 'primitive' populations. This cultural use could have exacerbated our evolutionary determined back problem.[1]

Evolutionary medicine, in sum, has inherited the holistic approach implied in actual evolutionary biology. To study why the body is not better designed required a wide approach that has to take into account heredity, development, behaviour, and natural and social environment. Evolutionary medicine, moreover, even if it could be seen as an experimental science based on genetic analyses, uses also a strong anthropological and ethnographical perspective (Trevathan, 2007). This derives from the fact that one of the most important ideas of evolutionary medicine is that our body and behaviour is still adapted to the Palaeolithic stage, because it represents the longest period of our history, therefore evolution and natural selection have not yet had enough time to modify humans to new environmental and social conditions determined, in particular, by agriculture and breeding. Evolutionary medicine bases many of its assumptions and theories on the mismatch between our evolved design and our actual condition. Anthropology, palaeoanthropology and ethnography of actual so-called 'primitive' populations play an important role in establishing the foundations of this theory.

Unfortunately we cannot enter into details here; it will be enough to give just another brief example, that of lactase persistence. The WHO (World Health Organization) classifies 'lactose intolerance' as a metabolic disorder, which is related to gastrointestinal symptoms caused by the consumption of milk in the majority of the adult world's population. Normally humans possess the lactase enzyme, which permits the digestion of milk, only when they are infants. In this period this enzyme is necessary to absorb mother's milk. As reported by Gluckman et al:

> But after weaning, production of the enzyme is largely switched off: most animals will never encounter large amounts of lactase again, so why waste resources

> synthesizing the enzyme? In most human populations, lactase is lost between 2 and 5 years of age (2010, p. 6).

However, some populations manifest the persistence of lactase also during adulthood. Gluckman et al. give us a clear explanation:

> Yet only a minority of the world's population continues to express lactase and is able to drink fresh milk in adulthood: they show 'lactase persistence'. This ability is genetically transmitted as a dominant trait, and in general lactase persistence in a population correlates with that population's history of cattle domestication. Although milk can be used by people who lack the enzyme – the lactose content of milk can be decreased by processes that encourage the growth of lactose-hungry micro-organisms such as by allowing it to sour or by making cheese – individuals who can digest fresh milk benefit from the additional energy obtained from the lactose. Thus, in the absence of major costs of maintaining expression of lactase it is easy to see how strong selection pressure for lactase persistence would have favoured the retention of this capacity into adulthood in cultures that developed cattle domestication (2010, pp. 6–7).

So, we can see that to explain the phenomena related to lactose intolerance and lactase persistence we need not only a genetic (the genes of lactase), but also a developmental (when and how lactase is lost or maintained) and a socio-cultural approach (necessary to understand *why* lactase persists in some populations).

One of the typical formulas of evolutionary medicine is that this new discipline studies traits, not disease, in the sense that it studies traits as they leave humans vulnerable to disease. Nesse, for instance, wrote that:

> Williams and I began by trying to find evolutionary explanations for diseases. We soon recognized that this was a mistake; with a few exceptions, natural selection does not shape diseases. Progress came when we shifted the focus to shared traits that leave all members of a species vulnerable to a disease—traits such as the appendix, the narrow pelvic outlet, and the limitations of the immune response. We began posing questions about vulnerability to disease in the form: 'Why has natural selection left this species vulnerable to this disease?' (2007, p. 416).

Evolutionary medicine, as evolutionary biology, studies the evolution of bodies and populations, breaking them down into 'phenotypic traits.' We cannot enter here into the problem of what is exactly a biological or phenotypic trait, because it is a complex and difficult theoretical question (see, for instance, Wagner and Laubichler, 2000). We can just give a general definition. In biology, a phenotypic trait is a physical attribute, or a life-history characteristic, or a behavioural characteristic (including characters and emotions) that could be inherited, environmentally determined or a combination of the two. Upright posture, for instance, is a physical and behavioural characteristic which we could define as a phenotypic trait. Evolutionary biology studies the evolution of upright posture in humans, while evolutionary medicine studies why and how upright posture leaves humans vulnerable to back problems.

Now, the study of a single phenotypic trait needs a holistic perspective, as already seen for the cases of upright posture and lactose persistence, in the sense that to understand its evolution we should know its genes, its development and how it is related to environment – also if this remains an unachieved goal in many cases for the lack of data. We need also to establish the relationship between this trait and all the others in the body.

Evolutionary medicine, more in particular, studies phenotypic traits as they are related both to adaptation and to disease, in the sense that it tries to find how an adaptive trait also determines, directly or indirectly, a vulnerability to a disease or a family of diseases. Nesse and Williams,

for instance, asserted that their 1994 book was based on the concept of adaptation by means of natural selection. Adaptations are those physiological and behavioural mechanisms by which we fight our pathogens, but also the mechanisms by which our pathogens escape to our defences. Adaptations, moreover, are never perfect mechanisms, but they have always some costs, limits or defects. The latter are at the base, for instance, of the mismatch between our design and the actual environmental conditions (Nesse and Williams, 1994, p. 4).

McGuire and Troisi, in their *Darwinian Psychiatry*, tried to explain psychiatric disorders with evolutionary models, gene-environment interactions, social and ethological studies. Evolutionary psychiatrists have to analyze all the factors that contribute to a 'behavior system,' the same factors that are essential for a holistic perspective: evolution, genes, development and environment. So, evolutionary psychiatry is not reductionistic:

> *In evolutionary biology, genetic explanations do not lead to reductionistic interpretations of behavior*. Genetic information is only part of the story of conditions. [...] Multiple intervening variables and social contingencies influence phenotypic expression, and these influences may be more or less important than genetic information. An in-depth understanding of conditions presupposes an understanding of each of these potential contributing factors (1998, p. 279).

In Stearns' *Evolution in Health and Disease* we find interesting discussions about heart diseases in terms of the genetic architecture of their susceptibility, of the relationship between genes, phenotypes and contexts, and in terms of development, for instance related to the 'foetal origins of coronary heart disease.' Genetic architecture is defined as follows:

> The genetic architecture of a trait is defined by the number of genes involved, their genomic positions, the number of alleles per gene, the relative frequencies of these alleles, the organization of allelic variations into genotypic variation, and the relationship between genotype variation and phenotypic variation. The relationships between genotype variation and trait variation involve dominance, epistasis, genotype by environmental interactions, and age- and gender-dependent penetrance. Studies of the genetic architecture of the anatomical, biochemical and physiological traits that are associated with the onset, progression, and severity of disease are central to understanding the genetic architecture of susceptibility to a common disease like cardiovascular disease (Kardia et al., 1999, p. 233).

Here we find the typical reasoning of evolutionary medicine with its holistic perspective, even if the study is principally focused on genes.

Evolutionary Medicine, edited by Wenda Trevathan, Euclid Smith and James McKenna (1999), has a most solid anthropological basis and is most broadly based on the concept of mismatch. Infant crying behaviour which could become a 'colic syndrome,' for instance, is studied with a comparative analysis of caregiving uses between western populations and the '!Kung San,' hunter-gatherers of Botswana (Barr, 1999). !Kung San's mothers carry infants constantly in their arms, or in a sling, while infants in the developed world often stay separated from their parents. !Kung San infants are kept upright, instead of supine. They are fed 'continuously,' three to four times an hour for one to two minutes/feed, rather than in a 'pulse' pattern as in western countries. Finally, !Kung San mothers give an immediate response to every cry, in contrast to western populations in which mothers deliberately refrain from responding. Given that !Kung San infants do not suffer from colic syndrome and given that !Kung San caregiving behaviour is probably more similar to that of our evolutionary past, the hypothesis is that modern caregiving uses are at the base of the exacerbation of infant crying behaviour. Colic syndrome has been long since interpreted by medical research as a gastrointestinal problem and a lot of biochemical and physiological studies have been made to understand its pathophysiology and pathogenesis, but all drug treatments have proved to be ineffectual and some even dangerous

(Lucassen et al., 1998). By contrast, sufficiently large changes in caregiving could be effective in treating or preventing colic (Barr, 1999, p. 43). This example proves again that evolutionary applications to health problems have the merit of giving a holistic perspective in which to integrate data from different fields (clinical observation, pathology and anthropology in this case) that otherwise remain disconnected.

Principles of Evolutionary Medicine (Gluckman et al., 2010) represents, in my opinion, a new phase of the discipline because, first of all, it is the first monograph explicitly designed for physicians. Secondly, it represents a step further because the authors have been able to integrate a new important perspective of evolutionary biology, that of so-called *EvoDevo*. The basic idea is, briefly, that the human foetus and infant respond to environmental stimuli by changing their developmental and growth trajectories (see, for instance, Gluckman et al., 2005, p. 671). This change can be directly adaptive, named 'immediately adaptive response,' but can have consequences later on in terms of susceptibility to some diseases. The change can also be predictive: the foetus, based on the information given by the placental environment, can set its future phenotype on the assumption that future environments will be similar to the placental one. These are named 'predictive adaptive responses.' This also can cause pathological susceptibilities if there is a mismatch between the prediction made in foetal life and the environment displayed in adult life. All these aspects come under the definition of 'phenotypic plasticity,' which is the capacity of a single genotype to exhibit a variable phenotype in response to environmental pressures (2005, p. 673). These 'epigenetic changes' are regulated by DNA expression and recent research has found that some of them could also pass through heredity for some generations, in a sort of heredity of acquired characteristics, such as some processes under the mechanisms of 'DNA methylation,' 'hystone modifications' and the 'association of small RNAs with DNA' (Gluckman et al., 2010, p. 88).

With evolutionary medicine we know that individual constitution is the result of the expression of an individual genotype that could give rise to very different phenotypes according to circumstances and environmental pressures. But all the characteristics that a phenotype expresses are a part of the *potentiality* of its genotype; otherwise they could not exist at all. Moreover, we know now it is effectively possible that a given acquired characteristic could became inherited for, at least, a few generations, by some known molecular processes. So, a given genotype could express an insulin resistant phenotype in response to foetal undernutrition at a given stage. The DNA methylation that determines this phenotype could pass to the next generation, giving rise to phenotypes characterized by higher adiposity than normal and so predisposed to obesity and diabetes (Gluckman et al., 2010, p. 202). The holistic character of evolutionary medicine is evident. To consider diseases in evolutionary terms implies the necessity to consider the phenotypic traits involved. This, in turn, implies the necessity to consider the evolutionary history of these traits in relationship to all of the body. Each phenotypic trait is the result, in fact, of an evolutionary history that involves the body as a whole: in terms of its genetic program, its development, its behaviour and its social and natural environment. Each phenotypic trait has an adaptive significance, past or present. Even if it is neutral, it can be related to other features that have adaptive significance. Each adaptation has some costs, or, being the result of different evolutionary mechanisms, is the result of some compromises. These costs or compromises could determine vulnerabilities to disease.

So, the concept of adaptation by natural selection seems able to explain why our bodies and minds are shaped as they are and why they carry on vulnerabilities to disease. In evolutionary medicine the unity of the mind-body system is not guaranteed by the fact that there is a correspondence between the body's shape and psychic character, but by the fact that the same *principle*, that of adaptation by natural selection, could explain the shape of both body and

mind. This concept, by consequence, could be the unifying principle that gives the framework to organize the separated disciplines of medicine, from clinical sciences to epidemiology to general pathology. As already stated in the first paragraph of this text, evolutionary medicine is holistic because holism is organic nature in its evolution. It is holistic also because it is a method through which to integrate data from different and separated disciplines through the principle of natural selection. It is holistic, finally, because to consider the body as a product of natural selection gives us a *new* knowledge of it, not recognizable by classical mechanistic approaches, that is, a body as a 'bundle of careful compromises.' The classical medical paradigm sees human beings as perfect machines, diseases as malfunctions or breakings, and doctors as repair men. Evolutionary medicine sees the body as intrinsically imperfect and continually adaptable, and diseases as the expression of costs of adaptations and defences, or past adaptations which have become harmful.

Holism in evolutionary medicine does not mean that natural selection, supposed to be at the base of evolution of health and disease, is the one and only principle of life, but it means that it is probably the most fundamental; without it life itself would not be understandable. This new discipline uses a wide spectrum of evolutionary explanatory models: some of them have nothing to do with natural selection, but it remains the case that this principle can be considered the basis of direct and indirect explanations of the widest number of cases, and the link between phenomena from apparently different domains of nature, such as those related to body and culture.

Conclusions

In their history of biomedical holism from 1920 to 1950, Christopher Lawrence and George Weisz pointed out that this approach was determined by the necessity of giving a 'synthesis' to the growing amount of data that invaded life sciences between the end of the nineteenth and the beginning of the twentieth century:

> Theoreticians of holism frequently talked about the need of synthesis to supplement or replace the dominant role of analysis. [...] At the simplest level, perhaps, 'synthesis' was used as a call to bring order and general principles to the rapidly growing, specialized scientific data that were inundating modern medicine. Between 1880 and 1920, the world of institutional medical science, fuelled by the growth of higher medical education, expanded at a remarkable rate. [...] 'Synthesis' in this context meant summarizing and making sense of all this new knowledge and bringing order to therapeutic disarray (1998, p. 3).

Evolutionary medicine was born in the 1990s, after half a century of incredible discoveries in the fields both of biology and of medical sciences. From the middle of the twentieth century molecular biology revolutionized life sciences with the discovery of DNA structure and the new technology of genetic engineering. The molecular revolution had a great impact in medical sciences because it permitted a deep knowledge of molecular mechanisms in cell metabolism, signalling and communications, and in terms of new diagnostic procedures and therapeutic possibilities based on molecular design of new drugs. These new paths, jointed with even more sophisticated technologies, also improved surgery and permitted the great success of transplantology. At the same time, evolutionary biology became more sophisticated in terms of mathematical models and some of the most difficult problems, such as those of animal behaviour, found new promising solutions. Genetic and epigenetic experimental data, finally, now permit also a deeper knowledge of evolution and the development of organisms. Evolutionary medicine emerged as the explicit attempt to find a framework to organize all these different disciplines and it has found in evolutionary biology the best science to carry on this theoretical unification.

Of course we cannot know if reality is based on a unique principle or element. This is a metaphysical question that cannot be tested. What we know, however, is that science works better when it is based on a unified model and principle to produce and verify hypotheses. Galileo thought that nature was written in mathematical language, Newton based his model on the principle of gravitation and Einstein on relativity. Darwin explained nature with a model based principally on natural selection. Every time that a unifying principle has come along, science has improved its capacity for explaining natural phenomena. As with these sciences, medicine also has continually searched for a unifying principle to explain disease. Humours, irritability, vital force and others have been used for this purpose. However, nowadays the principle that is working better to explain organic nature is natural selection. Maybe this same principle could also be effective in the explanation of disease. Our analysis cannot tell us if this is the right way. It can just tell that evolutionary medicine is a young science, but its assumptions came from the root of western medicine in its attempt to find a rational principle able to provide a scientific basis for our explicative models of reality.

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Notes

[1]During my fellowship at the IAS in Durham, Professor Sander Gilman gave a public lecture entitled: '*Stand up Straight': Posture, its History and the Meanings attributed to the Upright Body*. On this occasion Gilman reported also the old habit of thought according to which 'posture separates "primitive" from "advanced" peoples and the "ill" from the "healthy."' His annotation gave me the idea reported here that this habit could have had an effect on our vulnerability to back problems determined by the human evolutionary path. I take this occasion to thank Professor Gilman for the useful discussions I had with him.

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