Origins and History of Darwinian Medicine

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ABSTRACT

Contemporary Darwinian medicine is a still-expanding new discipline whose principal aim is to arrive at an evolutionary understanding of aspects of the body that leave it vulnerable to disease. Historically, there was a precedent; between 1880 and 1940 several scientists tried to develop a general evolutionary theory of disease as arising from deleterious traits that escape elimination by natural selection. In contrast, contemporary Darwinian medicine uses evolutionary theory to consider all the possible reasons why selection has left human vulnerable to a disease.

INTRODUCTION

Applications of evolutionary theory to medicine continue to grow in USA and European scientific communities. Starting in the early 1990's several articles and books proposed a new discipline, called evolutionary or Darwinian medicine (Williams and Nesse 1991, Ewald 1993, Nesse and Williams 1994, McGuire and Troisi 1998, Stearns 1999, Trevathan 1999, 2007, Stearns and Koella 2008). However, over a century ago other scientists tried to build an evolutionary theory of disease. This article reconstructs the historical precedents of Darwinian medicine and analyzes similarities and differences between the old and the contemporary approaches.

STATISTICAL ANALYSIS

An analysis of historical literature reveals that a group of physicians tried to construct a Darwinian theory of disease in the period from 1880 to 1940. I will call this period "Medical Darwinism" (Zampieri 2006a: 19-36). Inverting the phrase Darwinian medicine reflects the fundamental difference between the two approaches. Medical Darwinism conceptualised disease as resulting from characters that escaped natural selection, while Darwinian medicine analyzes disease as arising from vulnerabilities built and sometimes maintained by natural selection itself. I will use the term Darwinian medicine for the contemporary approach, rather than evolutionary medicine (which some authors prefer), because the term "Darwinian" implicates directly the theory of natural selection. The term "Darwinian medicine" was first used by Benjamin Ward Richardson in an article published in 1893 (Richardson 1893), but he was speaking about the medicine of Erasmus Darwin and without the suggestion of a new discipline. The terms "Darwinism" and "Darwinian" can have pejorative connotations; for some it conjures up visions of eugenics and Nazis. This article nonetheless uses these two phrases because they help to make the argument clear and because the name Darwin and its

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derivatives implicate directly the theory of natural selection, which is at the centre of the differences between the old and the new approaches. So, in this text Darwin, Darwinism and Darwinian are in some sort synonymous of natural selection theory. Of course, the theory of natural selection has profoundly changed over time. The theory of classical Darwinism (1860-1900) is different form classical Neodarwinism (1900-1960) and current Neodarwinism (1960-now) (see the Glossary). Medical Darwinism (1880-1940) uses at least two different theories of natural selection, while Darwinian medicine (1990-now) uses all aspects of evolutionary theory, including natural selection, drift, migration, etc.

Natural selection refers to the population effects of differential reproduction. This core principle has been applied in profoundly different ways in classical Darwinism, Neodarwinism, and current applications in medicine. These differences are the central focus of this article. Although Darwinian medicine embraces the application of the full range of evolutionary biology to all problems in medicine, my main thesis is that the new application of natural selection to understand vulnerabilities to disease is, at least from an historical point of view, Darwinian medicine's most important contribution. I use the term medicine, rather than, for instance, health science, despite some awkward limitations. For instance, the term medicine implies medical practice, however Darwinism has broader implications for research and for populations, for example epidemiology and public health. Again, the choice of terms is justified because the central argument is about the relationship between natural selection and disease. In my opinion, Darwinian medicine is significant because it proposes a new definition of disease, and a new kind of question about disease that provides a foundation for all medicine.

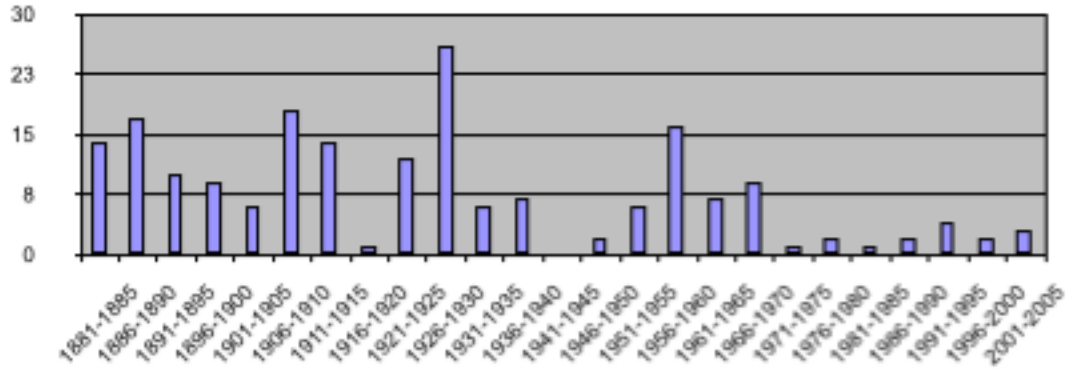
A brief catalogue of the most important works on medical Darwinism (1880-1940) provides an overview of the development of this intellectual movement. In the writings of Charles Darwin, for example, we often encounter the problem of the nature of disease; the question of pathological heredity was extremely important in his system of thought. In his time, hereditary disease was an important proof of the inheritance of variation, a necessary component of his theory of natural selection. It is interesting to cite an anonymous reviewer of Darwin's time: "The life of Darwin should possess a special interest for medical research, inasmuch as he and his work may in a sense be regarded as the product of our own profession" (anonymous 1888: 380). In his early notebooks many observations are tied to his father's medical practice (Bynum 1983). In *The Variation of Animals and Plants under Domestication* we find, in chapter XII, many examples of hereditary diseases in humans, animals and vegetables as proof of inheritance of variations (for a wider analysis of Darwin, see: Bynum 1983, Corbellini 1998, Zampieri 2006a).

In the period between the end of the nineteenth century and the first decades of the twentieth century, many monographs apply Darwinism to specific medical topics (Millican 1883; Maclagan 1888; Poulton 1913; Starr 1925; Roberts 1926; Nicolle 1930) or to the general understanding of human disease (Paget 1883; Mitchell 1888; Campbell 1889; Douglas Lithgow 1889; Bland-Sutton 1890; Nash 1915; Adami 1918; Ribbert 1918; Lwoff 1944; Haldane 1949). Reading these texts convinced me that from 1880 to 1940 there existed a movement (especially in England), to use Darwinism to better understand disease.

To verify this finding, We have analyzed the contents of two most important weekly English journals of medicine: *The British Medical Journal* and the *Journal of the American Medical Association*. At the time, they were the most important medical journals in England and USA, the countries in which medical Darwinism and Darwinian medicine developed. To test the hypothesis, I measured the frequency of the terms *Darwin, Darwinism, Evolution,* and *Evolutionism* in these journals from 1880 to 2000 (in reviews, letters and articles). Both journals collect weekly issue in two volumes each year, with a general index at the end of

second volume. Articles are indexed both by themes and authors. I located all articles with *Darwin*, *Darwinism*, *Evolution* and *Evolutionism* as a principal theme listed in the indexes of these two journals: from 1881 to 2003 for *The British Medical Journal* and from its origins in 1917 to 2003 for the *Journal of American Medical Association*. I then read each article to confirm that Darwinism was a central theme. Table 1 shows the results for *The British Medical Journal*.

TABLE 1
Number of articles on Darwinism in BMJ for five-year intervals, 1881-2005



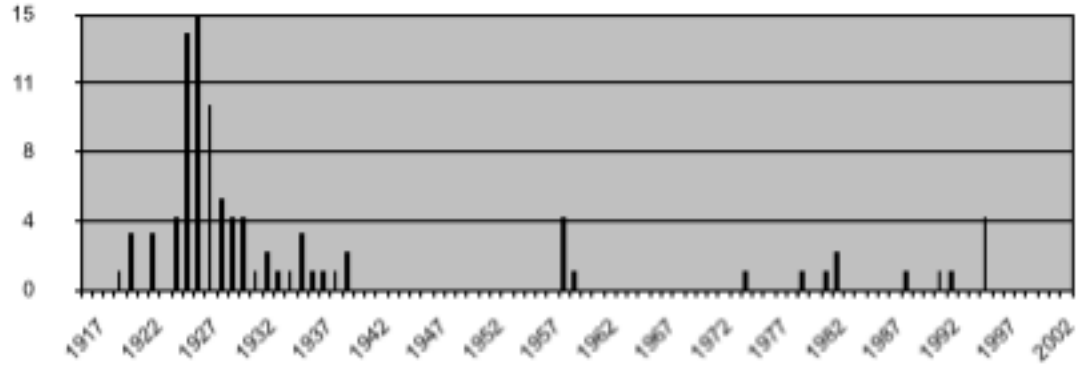
Reference: Zampieri 2006a: 253-253.

In the period between 1881 and 1931, physicians contributed many reviews, letters and articles on the subject of Darwinism and disease. In the fifty years between 1881 and 1931 we find that 128 articles were about Darwinism, while between 1931 and 2003 there were only 67. Between 1931 and 2003 almost all articles were reviews of books on evolutionary biology, such as the important Neo-Darwinian texts of Fisher, Haldane and Wright. Between 1881 and 1930, a more diverse collection of reviews, letters and articles directly on Darwinian interpretation of disease was published. The peak between 1951 and 1960 was caused by the 1958 Centennial of the presentation of natural selection theory by Darwin and Wallace at the *Linnean Society*. Those articles were not on medical Darwinism, but instead were reflections of the celebration. The period 1881-1930 saw additional publications related to the death of Darwin in 1881 and the Centenary of his birth in 1909. Many articles published for those occasions were mainly celebrative, but some also contained arguments concerning medical Darwinism (Zampieri, 2006a). Between 1931 and 1990, 59 articles were published on the subjects *Darwin, Darwinism, Evolution* and *Evolutionism*. Between 1991, the birth year of Darwinian medicine (Williams and Nesse 1991), and 2003, we find 9. If we don't consider the peak between 1951 and 1960, for the reasons explained above, we find that between 1931 and 1990 43 texts were published, while, between 1991 and 2003, 9 texts. This amounts to a frequency of 0,71 texts per year in the period between 1931 and 1990, and a frequency of 0,69 texts per year for the period of Darwinian medicine. Three facts are relevant to the small number of medical publications on Darwinian medicine. 1. The texts from 1990 to 2003 are almost all on Darwinian medicine, while the texts between 1931 and 1990 are more general. 2. Darwinian medicine was born in 1991 and has yet to achieve full expansion. 3. Contemporary Darwinian medicine is, for the moment, a mostly American phenomenon and it has more attention in biology than in medicine. Note: old medical Darwinism was mostly an English

phenomenon, while contemporary Darwinian medicine was born in the USA. Many difficulties attend the future task of conducting a social analysis concerning history of two disciplines in countries so different socially and politically; here to the goal is only to compare and contrast possibly related scientific ideas.

Table 2 illustrates the results for *The Journal of the American Medical Association* from 1917 to 2003.

TABLE 2
Number of articles on Darwinism in JAMA, 1917-2002



Reference: Zampieri 2006a: 254-255.

During the period of 90 years, only three articles were directly about a Darwinian interpretation of disease: two for the period of Medical Darwinism and one for Darwinian Medicine. In 1942, all mention of Darwinism stopped suddenly, for perhaps obvious reasons. Between 1900 and 1940, George Draper, one of the United States' most important constitutionalists, advocated studying disease by analyzing the human constitution in an evolutionary perspective. This approach was tied to eugenics. Draper and fellow constitutionalist Lewellys Barker, were members of the National Research Council's Committee on Heredity in Relation to Disease (CHRD). This eugenics-associated organization, founded by Charles Davemport, advocated eugenic policies. The horror of Nazi Germany's racially motivated politics caused a revulsion in American scientific and public opinion that ended American constitutionalism and medical Darwinism (Tracy 1992; monograph in prep. on this topic).

DARWINIAN MEDICINE AND MEDICAL DARWINISM

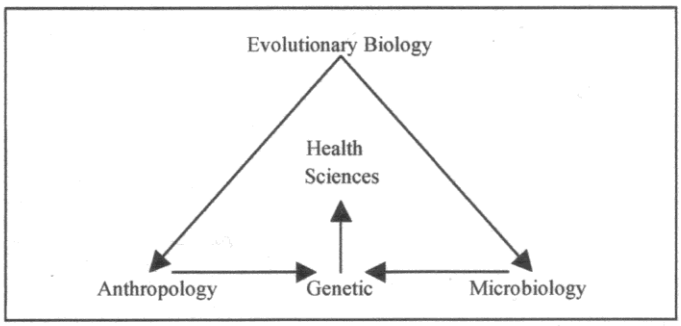
Contemporary Darwinian medicine is fundamentally different from what has come before. It addresses a wide range of categories of medical disorders and considers diverse causal factors. Three main monographs have initiated the discipline. The first, *Why We Get Sick*, was published in USA by Nesse and Williams in 1994, followed by a 1995 English edition under another title (Williams and Nesse 1994, 1995). *Evolution in Health & Disease*, edited in 1999 by the evolutionary biologist Stephen Stearns (Stearns 1999), and *Evolutionary Medicine*, edited in 1999 by the anthropologists Wenda Trevathan, James Mc Kenna and Euclid Smith (Trevathan et al. 1999). Both are now out with second editions (Stearns and Koella 2008, Trevathan et al. 2008).

All three texts present broad discussions about the theory of evolution, relying not only on natural selection, but also drift, migration, etc. Several well-established specialties in evolutionary biology are useful in medicine, such as population genetics, molecular evolution, evolutionary ecology, and anthropology. In addition, all three texts pose the new question about why bodies remain so vulnerable to diseases despite the actions of natural selection. We find theories about the evolutionary origin of vulnerability to cancer, virulence, allergies, sexual and mental disorders, neonatal, childhood or puberty disorders, and chronic degenerative diseases. We find some more detailed explications about, for instance, breast cancer, HIV, child abuse, substance abuse, schizophrenia, childhood asthma, coronary hearth disease, hypertension, diabetes and obesity. We find also some discussion about conditions not directly pathological, but with clinical relevance, such as menopause or senescence. We find discussions about normal capacities that lead to disease when then go awry, such as anxiety, pain, sadness, and guilt. Finally, we find some topics related to medicine, such as genetic geography and public health policy about drugs, infectious diseases and vaccines. The catalogue should be more wide and complex if we take into consideration not only these three texts, but also just a little part of the literature on Darwinian medicine produced after the foundation of the discipline.

Trying o establish some order in this complexity, a general structure can relate the more important disciplines and concepts in Darwinian medicine. A such simplifying framework offers a global perspective on the whole approach, with the risk of losing some details that do not fit well with the whole. This framework is useful here to facilitate comparison of the contemporary approach with the old one. Table 3 illustrates the essential structure of Darwinian medicine.

TABLE 3

Theoretical structure of Darwinian medicine



The pyramidal structure means that evolutionary biology, being at the peak, is the fundamental discipline whose concepts are applied by anthropological, genetic and microbiological perspectives. The evolutionary concepts for the health sciences are: natural selection, adaptation, coevolution, host-parasite arms race, defense and 'smoke detector principle', balance between costs and benefits, trade-off, genetic quirk, reproductive advantage at the expense of the individual, constraints, evolutionary legacy and mismatch (Williams and Nesse 1991, Ewald 1993, Stearns 1999, Trevathan et al. 1999). All these concepts refer principally to vulnerability, rather than to disease. The scheme doesn't means that Darwinian medicine is the historical outcome of anthropology, genetic and microbiology. It means that, in Darwinian medicine, each disease has to be studied finding an evolutionary vulnerability explained by an anthropological origin, a genetic determinism and/or a coevolutionary history with a pathogen. If we have a non-infectious disease, the main

hypothesis is: which kind of evolutionary vulnerability is implied? This hypothesis can be tested finding an anthropological origin, like: this disease is the byproduct of a specific human character or behavior (such as in the case of human environmental pollution, which induce a high risk of cancer). The hypothesis can be tested also with a genetic analysis, in terms of direct or indirect determinism. If it is indirect, the genetic involvement is in terms of determining susceptibility, predisposition, specific developmental trait or behavior. If the disease is infectious, we have to add also a history of coevolution between host and pathogens, both in terms of coevolution through several generations of host and pathogens, and in terms of coevolution between an individual host and several generation of a given pathogen in a single infection. This structure brings to new questions and answers in health sciences that in the past were not present. We have a new set of hypotheses, predictions and tests.

Nesse and Stearns list a broader range of disciplines: "The structure of evolutionary medicine is still defined by the different contributing disciplines": genetics, paleontology, microbiology and immunology, ecology, reproductive medicine, cancer research, physiology, anatomy, behavioral ecology, epidemiology, anthropology, and clinical medicine (Nesse and Stearns 2008: 41). Each of these disciplines can be ordered under one of the three fundamental approaches: anthropological, genetic and microbiological. This organization using just a few disciplines gives a simpler and better-defined structure that facilitates comparative and historical analysis, despite the risk of presenting a narrow vision of Darwinian medicine.

One or more of the basic approaches addresses each kind of pathology. Cancer, for instance, can be a disease analyzed both by anthropology as well as genetics, given the fact that the incidence of cancer varies with culture. Microbiology is the principal discipline for studying infectious diseases and the evolution of virulence, but genetic and anthropology also contribute. Studying the evolution of virulence requires diverse perspectives, including mathematical modeling, population biology, and genetics. Mental diseases can be explored by anthropology and genetics. For instance, addictions have become epidemic because of novel factors in the modern environment, but genetic variation strongly influences susceptibility.

This structure suggests three main categories of problems addressed by Darwinian medicine: *genetic disposition*, *disease of civilizations* and *evolution of infectious diseases*. The first category is named "disposition" to include all genetic factors that influence diseases. This includes not only directly genetic determined diseases, such as sickle cell anemia (Allison 1954, Hill at al. 1999), but also genetic factors that influence susceptibility to diseases such as cancer (Eaton and Eaton 1999, Greaves 2007), or addiction (Smith 1999, Saath 2005). Also, the pathologies associated with senescence are well analyzed by this approach (Kirkwood et al. 1999). The second, anthropological perspective is especially useful to analyze diseases of civilization – pathological conditions which arise, at least in part, from the mismatch between the body and contemporary environments. Several neonatal and childhood disorders, such as childhood asthma or infant colic, seem related to the way of living in stone age period or to the difference between old and modern environments (Trevathan et al. 1999). Finally, the third category, microbiology, gives insights into host-pathogen co-evolution with resulting traits such as virulence (Maynard Smith 1999, Moxon 1999). The contributions of these disciplines overlap. For instance, anthropology, genetics and microbiology are all required to understand the evolution of new pathogens due to new relationships humans-plants-animals in the modern environment (Strassmann and Dunbar 1999).

A further reduction may be useful for understanding Darwinian medicine. According to the two founders of the discipline, Williams and Nesse, a principal aim is to find an answer to the question: "[…] why our bodies are vulnerable to certain kinds of failure" (Nesse et al. 2006).

"The common answer – that natural selection just isn't powerful enough – is usually wrong. Instead, as we will see, the body is a bundle of careful compromises" (Nesse and Williams 1995: 4). From this perspective, the goal of Darwinian medicine is to use knowledge from genetics, microbiology and anthropology to explain why the body is vulnerable to a disease. Given the fact that this may be the more disputable and controversial idea of this article, we will discuss it in detail below.

With these points in mind, and with the knowledge of texts from the old period of so-called medical Darwinism (1880-1940), it is clear that the main problems addressed by medical Darwinism were more or less the same as those addressed by Darwinian medicine: genetic disposition, diseases of civilization, and the evolution of infectious diseases. Old medical Darwinism treated the problem of *genetic disposition* to disease in terms of diathesis (hereditary or acquired disposition to a family of diseases [Hutchinson 1884: 3]) (see the Glossary) and constitution (hereditary organization of an individual that determine health and disease [Draper 1924]) (see the Glossary). These two terms were different, but the concepts of disposition and predisposition to disease form the common background (as we can see in different medical encyclopedias and dictionaries: Dunglison 1848, 1874, 1904; Watson 1899-1910; Quain 1882). The authors who spoke about constitution at this time generally thought that diathesis was a special case of constitutional disease (Aitken 1858, 1866, 1880; De Giovanni 1891; Garrod 1927; Hurst 1927). Indeed, sometimes they spoke about diathesis and constitution as synonymous (Quain 1882; anonymous 1927a, 1931, 1932). Note that medical Darwinism is trying to explain why certain individual become ill. Darwinian medicine, in contrast, asks why all humans share characteristics that leave them vulnerable to disease.

Medical historians agree that the concept of diathesis (in its historically specific meaning) was born and declined during the nineteenth century (Ackerknecht 1982; Burgio 1995; Porter 1996). They also agree that this decline started during the second half of the century when solidism and localism in medicine won the battle against humoralism definitively and when experimental physiology and microbiology were born. However, starting in the 1880s, the concept of diathesis experienced a period of theoretical revival even while it was declining in the clinical world. Between the 1920s and 1940s, the word diathesis was again revived, this time to accompany the concept of constitution. This theoretical revival was due partly to the growth of Darwinian theory, and partially to a battle in which argued for the importance of internal constitutional causes of disease – that is, for diathesis and constitution—as opposed to microbiology.

In this long period (1880-1940), the doctrine of diathesis was gradually absorbed by constitutionalism, and these two concepts were at the centre of a new scientific attempt to understand human disease through heredity, biochemistry, evolution and anthropometry (e. g. Paget 1883; Hutchinson 1884; Lindsay 1909; Adami 1918; Draper 1925; Garrod 1927; Hurst 1927). Diathesis and disease-prone constitution were considered negative variations of the same biological nature of the positive variations fundamental to the construction of adaptations. Such individual variability was rarely considered by experimental physiology during this epoch (Hutchinson 1884; Campbell 1889); lack of attention to variation was one of the major points that medical Darwinists opposed in the new experimental paradigm (Zampieri 2006a). The following long citation of Garrod's famous article on diathesis and constitution show us: 1) the importance that evolutionary theory assumed in this period for understanding diathesis as a biological character, and 2) how evolutionist at that time saw diathetic diseases as negative variations that benefit the species, because they eliminate the unfit.

> Nor it is to be wondered at that the conceptions of our fathers regarding this subject seem to be obscure, nor that when we read what they wrote upon it we seem to wander in a

> fog; for when the doctrines were formulated the theory of evolution had not yet emerged; the existence of chromosomes and the importance of the germ plasm were not suspected; the laws of heredity were quite unknown, and hormones and vitamins had not been heard of. […]
> It is with unfavourable deviations that the student of diatheses is concerned, but if there were no beneficial ones there would be no evolutionary advance; progress could go no further; the species could, at best, be saved from regression. Unfavourable modifications tend to be eliminated, because they diminish the capacity of the organism to conform to its environment; and among the factors at work in the elimination of the unfit none is more potent than disease (Garrod 1927: 967-968).

Diathesis was often interpreted as a familial characteristic. It was considered unstable and could appear and disappear throughout different generations. Moreover, this familial characteristic was thought to follow Lamarckian heredity and the so-called blending heredity, that is the possibility of forming intermediate characters by the fusion of paternal and maternal types. We can find this interpretation, for example, in the entry for "Predisposition" in the Quain medical dictionary of 1882, written by the Darwinist Dr. W. B. Carpenter before genes were discovered (Carpenter 1882). Constitution, on the contrary, was conceived as built on Mendelian heredity and life experience and it determined the individual *reaction* to disease (Draper 1925; Hurst 1927).

Medical Darwinism from 1880 to 1940 explained the hereditary persistence of constitutional and diathetic diseases in terms of characters that escaped natural selection. They were seen as hereditary negative variations continually produced as part of natural variability. Hence, negative variability was the price of building evolutionary adaptations. By contrast, Darwinian medicine generally does not try to explain individual differences in vulnerability to disease, but instead it ask why natural selection has left all humans with characters that make them vulnerable to a disease.

Another field shared by medical Darwinism and Darwinian medicine is the *diseases of civilization*. Diseases of civilization depend directly on human manipulations of the environment, such as agriculture, pollution, overpopulation or unsanitary living conditions. They depend also on behaviors like alcoholism and prostitution. This topic is present in medicine from its beginning in the form of geographical pathology (Grmek 1963). However, while geographical pathology treats all of the influences of the environment on the organism, the concept of disease of civilisation implicates only the influence of the human environment. This discipline arose in its specific meaning in the nineteenth century, when industrialisation and overpopulation caused new health problems. The birth of Darwinism opened up the possibility that diseases of civilisation evolved and that they had a hereditary base.

In the first part of the twentieth century it was common opinion that diseases of civilisation depended only on environment. After the birth of Darwinism, the model started to consider heredity (Bynum 1983; Porter 1993). The concept of hereditary degeneration became the key to understanding the multitude of maladapted and sick individuals that new industrial society presented, and is was considered a necessary cost of progress. William Aitken, an English physician and supporter of Darwinism, wrote a medical handbook in 1858 that described physical degeneration as a "sad memorial of modern civilisation" (Aitken 1858: xci). In the edition of 1866, the old paragraph on degeneration became an entire chapter in which Aitken also discussed the mental and moral degeneration of the poor (Aitken 1866, vol. I: 132-148). For medical Darwinism, diseases of civilization were proof that natural selection didn't work in the case of man (e. g. Tait 1869; Campbell 1889; Haycraft 1894; Allen 1903; Lindsay 1909).

The English surgeon and gynecologist Lawson Tait (1845-1899) was one of the first physicians to accept Darwinian theory. He corresponded with Darwin, and he gave his inaugural address as the President of the Edinburgh *Hunterian and Medical Society* on Darwin's theory. He was also one of the first to propose that the theory of natural selection doesn't work in the case of civilized man (Tait 1869). As William Bynum writes, "Tait […] saw in 1869 the deteriorating constitutions of modern man as proof that medicine was keeping alive many who would otherwise have perished" (Bynum 1983: 47). Similarly, in a 1903 note on *Darwinism and the Increase of Cancer*, Dr. F. J. Allen wrote:

> In man's war against disease the fittest diseases must survive. We have learnt how to defeat plague, cholera, small-pox, tuberculosis, typhoid, and other diseases which formerly caused a large percentage of death; but we have not gained a corresponding power over cancer, and the result should be an increase in the ratio of deaths by cancer. In fact, many persons who in times past would have died of the former diseases should now escape them to die later of cancer. The medical art is directed against the elimination of the unfit [because it leave alive diseased people]; and one of its results must be to increase the relative number of persons of poor constitution and feeble resistance to disease (Allen 1903: 1527).

The idea of diseases of civilization and degeneration also formed the basis of a racial typology of disease and of the eugenic paradigm (Kevles 1985), a topic that is beyond the range of this article. Briefly, diathetic disorders were considered characteristics of the civilized elite, and included maladies such as hysteria, gout, and hypochondria, while primitive people and the industrial poor were thought to succumb primarily to acute epidemic diseases (Bynum 1983) with some diathetic diseases of the poor of secondary importance, such as alcoholic diathesis. To improve the species, the proposed solution was a program of eugenics. Eugenics ideas were promoted for decades before Francis Galton named the field in 1883. Its aim was to prevent the increase of disorders attributed to hereditary characteristics, such as insanity, alcoholism, and prostitution. These characteristics were prevalent in the industrial poor, so they bore the brunt of eugenic measures. For civilized elites, on the contrary, diathetic disorders were considered simply the price of the progress of civilization or, alternatively, the physical manifestation of vice, as in the case of gout, caused by an excess of food and drink (Porter 1993).

Contemporary Darwinian medicine also discuses the diseases of civilization, which it sees as caused by the mismatch between the body and aspects of the current environment that are vastly different from those in the environments where the human species evolved (Williams and Nesse 1991; Nesse and Williams 1994; Stearns 1999; Trevathan et al. 1999). This issue is foundational for understanding a broad range of diseases, from psychiatric disorders, to autoimmune disease, to obesity, diabetes, and cardiovascular disease and cancer. Such diseases result, at least in part, from ancient adaptations built by natural selection that are maladapted to modern environments. This has nothing to do with diathesis, constitutionalism, or the eugenic paradigm. Old medical Darwinism saw diseases of civilisation such as a failure of natural selection in case of man, while contemporary Darwinian medicine see these diseases as the by-products of old adaptations built by natural selection itself.

The last field in common between medical Darwinism and Darwinian medicine is the concept of *evolution of infectious disease*. At the time of old medical Darwinism, the germ theory was a new paradigm that had begun to dominate the field of infectious disease. Pasteur was a national hero in France and his theory proved its practical value. Medical Darwinist physicians tried to employ Darwin's theory of evolution to react against the power of the germ theory paradigm. The majority of these physicians were Englishmen. This is not surprising

given that the issue was seen as a battle between the heroes, Darwin and Pasteur, of two nations that had a poor relationship. It is important to note, however, that, Pasteur and Darwin never met, and there was no apparent rivalry between us (Bynum 1983).

The reaction of Darwinian doctors was for social as well as theoretical reasons. Microbiologists were new professional actors gaining power and importance with the decline of classical physicians. For medical Darwinism, the theory of evolution proved that germs evolved. This was considered a proof that the concept of specificity of infectious disease (one species of germs = one specific infectious disease) didn't have a real biological basis. Darwinian doctors believed that a germ could evolve from one species to another in the course of a same infection. Hutchinson also denied the necessity of germs for infectious disease, because an infection could be caused by individual diathesis (Hutchinson 1884). For microbiology, the external cause of an infectious disease, the germ, was postulated as much more important. Doctors who followed medical Darwinism considered germs at the same level as internal causes, that is the individual reaction determined by hereditary constitution. This was at the heart of the rise of the doctrine of diathesis and of the dawn of European constitutionalism. According to K. M. Millican, who in 1883 published a book entitled *Evolution of morbid Germs*, and W. Aitken, who between 1884 and 1885 published several articles in the *Glasgow Medical Journal* on the subject, the application of Darwinian theory made it essential to consider both the external and internal causes of disease, and the internal was generally more important than the external. It was also necessary to understand that infectious diseases evolved, and that an individual infection could change in character, as with the change from scarlet fever to smallpox (Aitken 1885). An anonymous note in *The British Medical Journal* supported Aiken's theory, despite that the lack of laboratory evidence for conversion of one type of bacillus to another:

> Those who believe in the germ-theory as applicable to most infectious, contagious, and miasmatic diseases, and, at the same time, adhere to the creed of the evolutionist, see no reason for supposing that pathogenic micro-organisms form an exception to laws which are applicable, it would seem, throughout Nature. And, though skeptical concerning many of the explications which have been advanced in this connection, we may yet allow that some amount of truth lies behind; and this despite the fact that the conversion of bacillis subtilis to bacillus anthracis in the laboratory has been abundantly refuted (anonymous 1886: 114).

Furthermore, for the English physician J. D. Adami and for other physicians of the end of XIX century, the evolution of bacteria was proof of the heredity of acquired characters. Bacteria evolved from a non-virulent to a virulent form via direct action of the environment on micro-organisms which then pass this modification on by heredity (Adami 1918). Also, the conception of hereditary acquired modifications contrasted with the microbiological theory of specificity: bacteria could quickly acquire new characters imposed by the environment, hence fixed species of bacteria could not exist.

However, medical Darwinism and microbiology were not always in conflict. The famous English surgeon James Bland-Sutton, in his *Evolution and Disease*, took an intermediate position. External and internal causes were of the same importance and the theory of evolution was not in conflict with the theory of specificity, because the fact that species evolve does not mean that species do not exist (Bland-Sutton 1890). The definitive reconciliation between Darwinism and microbiology most likely came with the French bacteriologist Charles-Jules-Henry Nicolle (1866-1936). According to Nicolle, micro-organisms evolved in the same way as other natural populations, and his findings refuted the idea that one bacterial species could change into another (Nicolle 1930, 1933).

In any case, medical Darwinism never tried to uncover the action of natural selection in mediating the conflict between host and parasite. Also, while many physicians spoke of adaptation in relation to the evolution of virulence, they did not see adaptation and natural selection as related. According to Adami, for instance, the evolution of virulence was not an adaptation built by natural selection, but a phenomenon of acquired characteristics. In contrast, for contemporary Darwinian medicine the evolution of infectious disease is the result of the conflict between two adaptive systems built by natural selection, those of host and parasite. Moreover, infectious diseases continue to exist because pathogens reproduce more quickly than human individuals so they gain new adaptations more quickly than humans can adapt. This has important implications in drug and vaccine design (Nesse and Williams 1994; Levin and Anderson 1999, McLean 1999).

In general, in the field of predisposition to disease, of diseases of civilisation, and of infectious disease, medical Darwinism conceptualises disease as hereditary or acquired variation with no necessary, direct connection with natural selection. Disease was a negative variation produced by natural variability and maintained by virtue of its capacity to escape the elimination by natural selection. While the main problems of medical Darwinism were the same as those of Darwinian medicine (diseases of civilization, heredity disposition, evolution of infectious disease), there are at least three major differences between the old and new approach:

1) Medical Darwinism often had an ideological approach that is absent in Darwinian medicine. Medical Darwinism was implicated in the eugenics movement (see, for example, Tait 1869) and in debates on the metaphysical consequences of Darwinian theory (see, for example, H. Hutchinson 1946: 217-219; Haeckel 1866; Lombroso 1869), while Darwinian medicine is not. Darwinian medicine can be probably implicated in other ideological questions, but surely not these.

2) Medical Darwinism configured itself as a reaction against microbiological approach and experimental physiology, while Darwinian medicine does not.

3) Medical Darwinism explained disease as a characteristic that escapes natural selection, while Darwinian medicine investigates the action of natural selection in determining, directly or indirectly, disease.

4) Medical Darwinism was trying to explain why some individuals get a disease. Darwinian medicine instead tries to understand why all humans are the same in ways that leaves them vulnerable to a disease.

THE OBLIVION OF DARWINISM IN MEDICINE

As we have seen both in bibliographical resources and in statistical analysis, between 1941 and 1991 medical doctors neglected the study of Darwinism in medicine. The historical causes of this 'oblivion' and of the '*renaissance*' represented by contemporary Darwinian medicine deserve a deep monographic analysis. Here we would like to present a preliminary list of the more important causes.

1) The oblivion of Darwinism in medicine started with the period of crisis of Darwinism in biology at the beginning of the twentieth century (Huxley 1942). Followers of the constitutional paradigm in Europe and USA maintained Darwinism in medical thought until 1940s, as we have seen. However, in the first decades of the twentieth century, medicine seemed to be increasingly influenced by a Lamarckian concept of heredity, while Darwinism was in relative eclipse (Zampieri 2006a).

2) The oblivion of Darwinism in medicine coincided with the Flexner reform, which focused most medical research on experimentation (Lawrence 1993; Corbellini 2002). In 1922 the

American geneticist William Bateson (1861-1926) still thought that Darwinism was not an experimental science (Mayr 1982). Darwinism and medical Darwinism were based on a different model of knowledge, not strictly experimental, but empirical in a wider sense, that is, based on observation and induction. Moreover, evolutionary explanations are often multicausal, while the ideal of medicine, at least from its experimental foundation, has always been to find only a given specific cause for a disease. This multicausal approach probably has offended the cognitive medical preference for monocausal explanations (Nesse 2005). The experimental paradigm, finally, probably implemented the vision of body like a machine produced by an engineer, while Darwinian approach sees the body like a "bundle of compromises".

3) In the first decades of twentieth century, the teaching of Darwinism was forbidden in several US states: in 1926 in Mississippi and North Carolina (anonymous 1926a: 960; anonymous 1926b: 1704) and in 1928 in Kentucky (anonymous 1928: 298-299). In 1927 Florida and Arkansas tried to forbidden it (anonymous 1927b: 734; anonymous 1927c: 653). Even today, battles continue that limit the teaching of evolution in the USA, even if they do not prohibit it.

4) The oblivion of Darwinism in medicine was also caused by the fact that, from the end of the nineteenth century, medical thought concentrated above all on the direct causes of a disease in an individual, while Darwinism focused attention on historical causes. Medicine, in the first half of the XX Century, started to consider the reaction of an organism to disease or stress with homeostatic mechanisms (Cannon 1916, 1929, 1932) and the stress response (Seyle 1950). These mechanisms allow the body to adapt to its environment, but their evolutionary history was rarely considered. Darwinism's approach, moreover, from the beginning of the twentieth century, viewed the organism as a machine that undergoes evolutionary modifications that construct new adaptive traits by changes in the germ plasm. This was perceived as a conceptualization of the human body as an organism that is passive in the face of external or internal threats such as disease, while, to the contrary, medical thought considered the human body to be a machine that reacts actively in face of disease. Moreover, at this time, human behavior seemed impossible to understand in Darwinian theory, because behavior itself was not seen as a product of natural selection (McDougall 1927, 1930, 1933).

5) The US Surgeon General declared in the mid-1950's that the war on infectious disease was over (Nesse and Stearns 2008: 36). This idea probably bring medical doctors to neglect the possibility of the emergence of new diseases and so the evolution of infectious diseases.

5) Finally, the problem of eugenics and its association with Nazi policies was a profound cause of the oblivion of Darwinism in medicine after World War II (cf. Kevles, 1985).

THE DAWN OF DARWINIAN MEDICINE

Darwinian medicine arises now thanks to several new conceptual refinements of natural selection theory.

1) The first is that natural selection works at the level of genes, not that of individuals or species (Fisher 1930). This new approach allowed us to understand that natural selection cannot make a perfect machine and it does not shape the health and happiness of individuals or a species, it depends only on the reproductive success of genes. This was also the first step to understand the problems of altruism, sexual selection, and senescence (Williams 1957; Hamilton 1964; Wilson 1975; Cronin 1991).

2) The other modification was the concept of genetic pleiotropy, which permitted the understanding that some genes can have different effects, both positive and negative (Haldane

1949). This also permitted the formulation of the first theory of senescence based on the natural selection of genes (Williams 1957). It was important also the development of the concept of trade-offs, a sort of phenotypic analogue of pleiotropy. Trade-offs between traits is one of the most important explanations of vulnerability to diseases. Nesse and Williams shared the interest of the evolution of senescence at the beginning of their collaboration. This topic was the central argument around which developed the first ideas of Darwinian medicine.

3) Darwinian medicine, moreover, emphasizes the role of natural selection in shaping and maintaining adaptations (Williams 1966). Far from implying perfection, because adaptations are products of natural selection, they are always imperfect compromises. The work of natural selection is not perfect, it is a *bricolage* (Jacob 1970). Every trait has costs and benefits, and the costs may leave organisms vulnerable to disease.

The development of Darwinian medicine was favored also by advances in several biological specialties.

1) Genomics, in particular sequencing and new strategies for assessing signals of selection.

2) Evolutionary anthropology, in particularly from the second half of the 20th Century.

3) From the 1960's, evolutionary biologists started to use new techniques to study bacteria and viruses (Mayard Smith et al. 2000: 1115).

The birth of Darwinian medicine was also indirectly favored by independent changes in medical thought.

1) First, it was favored by the relative concept of disease (disease is a social construction, rather than an ontological phenomena, so it doesn't exist neither a pure disease nor a pure state of health) employed by psychiatry from the beginning of the twentieth century and fully developed in the last part of the century (see, for instance, the work of Oliver Sacks). Darwinian medicine is in the same line of thought, recognizing that all traits have advantages and disadvantages and defensive responses such as pain and fever, can be useful. The advancement of Darwinian medicine is to put this relative concept in an evolutionary perspective. It is probably not by chance that one of the two founders of Darwinian medicine, Randolph Nesse, is a psychiatrist.

2) Its emergence was also helped by the development of medical ecology in the second half of the twentieth century. Jacques May defined disease as a:

> […] maladjustment to the environment to which numerous factors contribute; disease, therefore, becomes an anthropological phenomenon with a geographical distribution. […] Disease, any disease […] can never occur without the combination of three orders of factors converging in time and space, that is, there must be stimuli from the environment, there must be responses from a host, and there must be the conglomeration of thoughts and traits that we call culture (May 1961: v, xvi).

As we can see, the factors of time and space, fundamental in an evolutionary perspective, also became important in the ecology perspective. Again, it is probably not by chance that Paul Ewald, one of the main precursors of Darwinian medicine (Nesse and Williams 1994), spoke about the necessity of an ecological approach in infectious disease (Ewald 1980). Ewald was also the first researcher to speak with George Williams in the 1980's about the potentiality of a new discipline as evolutionary medicine (personal communication). His *Evolution of Infectious Disease* remains one of the most important books on Darwinian medicine (Ewald 1993).

3) Darwinian medicine was also born in consequence of a historical event that caused a great reaction in medical world: the emergence of HIV, which forced physicians to think about the evolution of infectious disease and the possibility that a new infectious disease can emerge at any time (Lederberg 1988; Ewald 1994, 1999).

4) Finally, its birth was helped by the development of medical genetics (Neel 1962, 1982, 1994; Bodmer and Cavalli Sforza 1976; Childs 1988, 1996, 1999), which forced medicine to think about evolutionary mechanisms responsible for human genetic differentiation.

THE THEORETICAL FRAMEWORK OF DARWINIAN MEDICINE

Between 1960 and 1990 precursors of Darwinian medicine appear in several fields. The English physician John Harper published many studies on the evolutionary interpretation of disease between 1960 and 1970 (e. g. Harper 1975). Renè Dubos worked on the relative concepts of health and disease (Dubos 1965). Ewald, as noted, discussed the evolutionary interpretation of infectious diseases, Margie Profet elaborated an evolutionary theory of some immunological phenomena (Profet 1991), and David Haig applied the theory of kin selection and parent-offspring conflict to pregnancy and other issues in reproductive medicine. Finally, Eaton was a pioneer in evolutionary anthropology (Eaton 1988, 1990).

There are some established methodologies used in medicine long before the advent of Darwinian medicine, such as population genetic, the study of antibiotic resistance and the techniques to trace phylogenies. Darwinian medicine has surely profited by these methodologies, but it rest different in its questions and researches. Darwinian medicine, in fact, asks questions about adaptation and these questions needs answers not only quantitative. For testing hypotheses about adaptation Darwinian medicine uses a wide range of methodologies, from genetic to comparative anatomy, but what is really new for medicine is the set of starting questions. Questioning about the adaptive value of traits which leave us vulnerable to disease is, historically, a new question and lead up to new researches programs and, possibly, to new answers.

From 1991on, an increasing number of articles on different aspects of Darwinian medicine appeared (for a summary until 2001: Stearns and Ebert 2001) and many laboratories in Europe and U.S.A. became involved in evolutionary approaches to diverse medical and biological problems. The rapid continuing growth of such work can be followed on the web at http://evolutionandmedicine.org. My purpose here is to discuss only Darwinian medicine's theoretical structure, and in particular the relationship between vulnerability and natural selection that I propose as the core of this approach.

Between the authors of Darwinian medicine, Randolph Nesse has been surely the most active on the attempt to define theoretically the nature of the new discipline. So it is normal that we start form his thought for trying to find the theoretical specificity of Darwinian medicine. In his chapter of the second edition of *Evolution in Health & Disease*, Nesse wrote:

> Williams and I began by trying to find evolutionary explications 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?" (Nesse 2007: 422).

One consequence is that Darwinian medicine has not generally focused directly on disease, but rather on vulnerabilities to diseases. These vulnerabilities are not, generally, specific traits of given individuals, they are universal traits that belong to all human mankind, such, for instance, the limited ability to control cancerous cell replication. This tendency of Darwinian medicine toward the general, rather than the individual, is also confirmed by the fact that Nesse always cite in his articles, regarding the question of disease causation, the distinction

between proximate and evolutionary explication and, more particularly, the "Tinbergen's Four Questions":

> *Proximate Questions*
> 1. *Mechanism* – What is structure and composition of the trait and how does it work?
> 2. *Ontogeny* – How does the trait develop in an individual?
> *Evolutionary Questions*
> 1. *Phylogeny* – What is the evolutionary history of this trait?
> 2. *Selective Advantage* – What selection forces shaped this trait? (Nesse 2007: 422; Tinbergen 1963)

According to Tinbergen, a complete biological explanation of a trait requires an answer to each of these four questions. According to Nesse, traditional medicine has paid attention until now only to proximate explanations, while Darwinian medicine focuses on evolutionary explanation. If we analyze the four questions, we can propose the idea that *Proximate Questions* are focused on individuality, because they try to explain a trait observing the structure, function and development of the trait itself in a given individual independently from the eventual sharing of this trait by several individuals in a given population, while *Evolutionary Questions* are more general, because they are focused on evolutionary history and selection forces that can be applied only studying a trait that at least a part of a given population share. If a trait is possessed only by a single individual, for instance, a new mutation, there is no past evolutionary history; selection has not had a chance to act.

So we come again to the core characteristic of Darwinian medicine; it tries to find evolutionary explanations for shared characteristics that leave all people vulnerable to a disease. Explaining a disease in an individual is a very different matter that almost always involves the complex interactions of individual differences with environmental factors in sequences that may be unrepeatable. However, although we all share vulnerabilities that are explained by evolutionary history, those vulnerabilities also vary among individuals. Even an infection can be seen as the result of an individual history – the exposure to a pathogen that vary interacting with an individual's particular constitutional susceptibility.

The focus on explaining why individuals share traits that make us all vulnerability, rather than differences that make some people get sick, does not mean that Darwinian medicine ignores the challenge of curing of sick patients. The population thinking that is intrinsic to a Darwinian approach emphasizes that it is a mistake to think there is some one version of a trait is "normal." Traits are characterized by a spectrum of possible variations or alternatives. Moreover, individual variability is not determined by genes, it is plasticity arising from interactions between genes and environments. Much plasticity, such as tanning, reflects systems shaped by natural selection to adapt individuals to changing environments. Diseases are often related to this individual variability; individuals at the extreme part of the spectrum of variations are more liable to disease. From an evolutionary viewpoint, the singularity of each individual is not an exception, but an expectation.

A recent article by Nesse and Stearns argues that the concept of vulnerability accounts both for why we are all the same and for why there are individual differences (Nesse and Stearns 2008: 32). Again, infectious diseases provide a useful example. From one side, we recognize that all humans are vulnerable to malarial parasites because we evolve more slowly than they did. From the other side, individuals differ in their vulnerability for good evolutionary reasons. Individuals who are heterozygous for the sickle cell allele have a mile anemia but they are protected against malaria, and so the sickle cell allele is more frequent in malaria endemic zones (Allison 1954). Finally, the evolutionary tools of phylogenetic analysis make it possible to

trace the evolution of a given infectious disease in a single individual, following the rise of new mutants during the course of disease (Maynard Smith et al. 2000).

Going further into the relationship between natural selection and vulnerability, Nesse and Stearns follow the lead of Barton Child (Childs 1999), saying:

> Bodies are vulnerable to disease – and remarkably resilient – precisely because they are not machines built from a plan. They are, instead, bundles of compromises shaped by natural selection in small increments to maximize reproduction, not health. Understanding the body as a product of natural selection, not design, offer new research questions and a framework for making medical education more coherent (Nesse and Stearns 2008: 28).

Of course, they do not mean that the body is anything more than flesh and blood. Their point is that natural selection doesn't construct bodies the way an engineer constructs a machine; it doesn't have a goal, it does not follow any plan and it can never start afresh. A common metaphor is rather that natural selection works like a *bricoleur*, but natural selection doesn't follow any plan at all; it is 'only' the consequence, of different reproductive success of individuals. The most accurate definition, in my opinion, is in an article of Stearns and Ebert: "Natural selection on a trait is the correlation between variation in the trait and variation in reproductive success" (Stearns and Ebert 2001: 427). At its root, natural selection is the consequence of differential reproduction of genes. And here we have probably the ultimate explanation of individual vulnerability. Genes become more frequent if they create bodies that reproduce more than other individual. Genes don't shape the happiness or health of organisms and species, they just become more common if they are in individuals with higher than average reproductive success. Such individual tend to be healthy, but a gene that increases reproduction at the expense of health will nonetheless tend to become more prevalent. Like larger traits, alleles have costs and benefits, one cost being a vulnerability to one or more pathologies.

At the end of this analysis, I believe that the core of this science can represented by three fundamental causal processes:

1. natural selection›adaptation
2. adaptation›vulnerability
3. vulnerability›disease

The critiques that have arisen after its foundation concentrate above all on the first and on the third causal relations, as we will see. Adaptation›vulnerability is not problematic. Every biologist or physician should know that an adaptation is not the expression of perfection and that, by consequence, every adaptation has some elements that could be called defects, or at least suboptimal. This relationship doesn't mean, of course, that an adaptation *is* a defect.

Concerning the first process, Williams and Nesse in their first article on Darwinian medicine cite the *adaptationist program* and say that this programme can also be useful in medicine (Williams and Nesse 1991; Nesse and Williams 1995, 1997). "[…] the adaptationist program" – write Williams and Nesse – "predicts otherwise unsuspected adaptive processes that can be searched for and, if found, described" (Williams and Nesse 1991: 3). Nesse, even before the collaboration with Williams, tried to find some adaptive significance of emotions that leave the human body vulnerable to disease (Nesse 1984), and he continues to pursue such work in psychiatry today (e. g. Nesse 2002, 2004). Williams and Nesse, moreover, give some important indications as to how this program can be applied to medicine (Nesse and Williams 1999: 19).

The adaptationist approach has aroused criticism. The most famous was expressed by Gould and Lewontin in an article that appeared before the advent of Darwinian medicine (cited

by Williams and Nesse): *The Spandrels of San Marco and the Panglossian Paradigm: A Critique of the Adaptationist Program* (Gould and Lewontin 1979). They viewed the adaptationist program as proposing an adaptive history for each trait, and they argued that this is a mistake because organisms are integrated wholes. Moreover, they emphasized the necessity of separating the current utility of a trait from its evolutionary origin and the prevalence of neutral or harmful characteristics that are epiphenomena. Finally, natural selection and adaptation must be considered separately, they say, because adaptation can be the product also of the constraints of evolutionary process, like the limit of genetic variability. Ernst Mayr, in an article entitled *How to Carry Out the Adaptationist Program?* (Mayr 1983), reminds us that the adaptationist program does not insist that adaptation is built always and only by natural selection. In the practice of Darwinian medicine, the *adaptationist program* tries to find the adaptive significance of the vulnerability to disease. So it does not imply that adaptations are perfect, nor does it imply that drift is unimportant. The deterministic and atomistic approach criticized by Gould and Lewontin is not always the approach of the *adaptationist program*. As Mayr notes, the adaptation of an organism is determined by the totality of its traits and their interactions. Analyses of specific traits are preferable from a scientific point of view. These analyses can be integrated into a subsequent comparative analysis of traits. In some cases, however, the specific analysis must be abandoned (Mayr 1983: 329). In medicine, specific analysis of a disease (that is, localism and solidism in the consideration of pathology) was the first step that transformed medicine into a more scientific discipline. But this doesn't necessitate the abandonment of the consideration of a disease as a reaction of an organism as a whole (for a further analysis on the concept of adaptation and the debate around it, see: Dobzhansky 1956, Williams 1966, Lewontin 1978, 1979, Segerstråle 2000: 101-126).

At any case, speaking only about adaptation and disease can be misleading, because the concept of adaptation itself is problematic in different ways. In fact, this concept seems imply that adaptation correspond to a machinery that is well designed and useful for individual. In reality, in biological world simply doesn't exist a perfect adaptation and in each case it should be preferable to speak about maladaptation, in the sense that each organic trait that can be defined as an adaptation has some aspects functional and some other useless or harmful for individuals. Nesse, in a playful reference to the title of Williams' 1966 book, has written about "Maladaptation and Natural Selection" as the core of Darwinian medicine (Nesse 2005); this makes sense only if we consider that natural selection is the effect of variations of reproductive success (RS) of genes in bodies interacting with environments. If we consider adaptation like a trait produced by an evolution based on RS of genes, the phenotypic outcome has to be almost always a maladaptation, because RS of genes is not directly connected with health, happiness and functionality of individuals. The best examples are genes that augment fertility, but which also harm health, such as those responsible of senescence (Williams 1957).

The RS of genes depend obviously of RS of phenotypes in a given environment, so the outcome of this relationship is always a compromise between the needs of genes and phenotypes, but, given the fact that the RS of genes is always the crucial element, the compromise is always unbalanced in detrimental of phenotypes and their relation with environment. So, we can probably distinguish between a genotypic adaptation, which is always reproductive success, and a phenotypic adaptation, that is rather a maladaptation. This idea can explain also the permanence of trade-offs, the adaptive change in a trait correlate with a harmful change in another trait of minor importance. In this case, the RS of two genes or groups of genes (one for the adaptive trait and one for the harmful) determine the permanence of the two phenotypic traits despite this is not optimal for the individual (the

question here is simplified, because there can be also a conflict between RS of genes or groups of genes, not only between genes and phenotypic traits).

The second process which was criticized is vulnerability›disease. In this case, it means hereditary vulnerability, otherwise it is not a question of evolution. This relation has the risk, according to some authors, of considering only the genetic factors in disease and forgetting the epigenetic phenomena which can give rise to disease (Corbellini 1998). Darwinian medicine, as we have seen, isn't directly interested in why an individual gets sick, but rather in the vulnerabilities in the human species that can give rise to disease. Epigenetic mechanisms are certainly formed and maintained by evolution, but those which give rise to disease are more often connected with individual cases. From its experimental foundation in the second half of the XIX Century, medicine seems more involved with laboratory data then whit the personal history of patients. Starting from the beginning of the XX Century, some doctors have proposed a medical approach more individualized, with a corresponding critic of a medical approach based on experimental data and general laws. It seems impossible to conciliate in medicine an individual approach with a nomotetic approach based on general laws, but Darwinian medicine offer a new way to create a *science of individuality*.

Old medical Darwinism tried to give a scientific basis to the concept of individuality through the concepts of diathesis and constitution in an evolutionary context. Diathesis and constitution were concepts strictly tied to an individual determination, although some physicians wrote about universal diathesis (Zampieri 2006b). This attempt was different from other twentieth-century attempts to reconstruct individuality. Whereas these latter attempts, such as *daseinanalyse* (Biswanger 1957), philosophy of Canguilhem (Canguilhem 1966) and medical ethics (Lefève 2000, Benincasa 2002), tried to reconstruct individuality without a reference to general laws, the attempts of old medical Darwinism tried to reconstruct the general biological laws that permitted the existence and expression of the individual laws themselves. The difference between the concepts of diathesis and constitution can't be examined here; it is sufficient to say that students of diathesis and constitutionalists between 1880 and 1940 spoke always of biological laws and that their explicit aim was to change the clinic into a *science* of the individual sick person (e. g. De Giovanni 1891). Darwinian medicine has gone further. It presents itself not as a clinical, but as a basic science which can unify the branches of medicine. Its explicit aim is not to understand why and individual gets sick, but why the human species has vulnerabilities which are maintained by evolution and which can be at the base of disease. In this way, Darwinian medicine can be seen as an approach that moves away from the individual and toward the general, and thus can be seen as working in coordination with the move toward standardisation in twentieth-century scientific medicine. This doesn't mean, as we have already said, that Darwinian medicine doesn't have a practical value in clinical medicine. Its central concept, vulnerability, accounts both for why we are all the same and for why there are individual differences (Nesse and Stearns 2008: 32). Standardization, in Darwinian medicine, means that also individual diseases can be understood by the general laws of evolution.

Medicine is a science that more than any other is confronted with the problem of practical effectiveness. After all, most people are not concerned with medicine's involvement with the ontological or existential truth of disease, but with the efficacy of medicine against disease. In this sense, it is necessary to re-evaluate the process of standardisation of medicine against which the critics of the individualistic approach are concerned, and it is also necessary to support Darwinian medicine in its theoretical framework.

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