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MEDICINE, EVOLUTION, AND NATURAL SELECTION: AN HISTORICAL OVERVIEW

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ABSTRACT

Contemporary Darwinian medicine is a still-expanding new discipline, one of whose principal aims is to arrive at an evolutionary understanding of those aspects of the body that leave it vulnerable to disease. Historically, there was a precedent for this research; between 1880 and 1940, several scientists tried to develop some general evolutionary theories 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 humans vulnerable to disease.

MEDICINE AND EVOLUTIONARY BIOLOGY: STATISTICAL ANALYSES

MEDICINE and evolutionary biology are both interdisciplinary fields, but in a profoundly different way. Medicine is a practice that borrows its basic concepts from other scientific disciplines so as to give coherence and repeatability to its actions.

Based on the curing of sick individuals, it takes from theory only what is applicable. Focused on the effectiveness of its actions, it cares less about the truth of its theories. It is interested in proximate causes of phenomena, because it is only to these that it is possible to act and react, and, for this reason, it is mostly related to scientific disciplines fo-

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cused on proximate causes (e.g., anatomy, developmental biology, and physiology). Evolutionary biology, in contrast, is an ensemble of theories for understanding the changes in living forms, and it has only recently started to find direct application. It is based on an idea—that of organic evolution—that is expressed in very abstract terms. Evolutionary biology is interested principally in remote or evolutionary causes, and its focus is on populations rather than individuals.

Given these differences, it seems that we might exclude *a priori* the possibility of an evolutionary medicine—that is, of an interdisciplinary field in which the concepts of evolutionary biology are applied for the cure of sick individuals. However, history shows us something different. There are two historical periods in which medicine and evolutionary biology cooperated to build evolutionary theories of disease that were eventually applicable to the curing of sick individuals—two periods in which Darwinism was sometimes an applied science and medicine a theoretical system, in which Darwinism became a science of individuality and medicine a theory of populations, and in which a network of schools and ideas existed whose complexity counted in favor of, rather than against, the fecundity of this approach.

As many monographs attest, there was a constant interest in evolution and disease on the part of doctors in both Europe and America between 1880 and 1940. Some of these monographs were devoted to a specific medical topic, such as *diathesis* (see Glossary) and *bodily constitution* (see Glossary) considered in evolutionary terms (Beneke 1878; Hutchinson 1884; De Giovanni 1891; Fouillée 1902; Pende 1922; Draper 1925; Kretschmer 1925; Garrod 1927; Hurst 1927; Castaldi 1928; Hammond 1934; Bauer 1942), the *evolution of infectious diseases* and *immunology* (Roux 1881, Aitken 1885; Maclagan 1888; Metchnikoff 1892, Millican 1893; Poulton 1913; Adami 1918; Nicolle 1930, 1933), or *diseases of civilization* (Tait 1869; Paget 1883; Allen 1903; Lindsay 1909). Others were dedicated to the general evolutionary 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). Among other interesting topics, often related to diseases of civilization, were the evolutionary nature of the human brain and the question of cancer (Jackson 1887; Roberts 1926). I refer to this time period (1880–1940) as medical Darwinism (Zampieri 2006, 2007, 2009a).

Within British and American medicine, I have tried to verify the consistency of the old medical Darwinism by a statistical analysis of two of the most important weekly medical journals: *The British Medical Journal* and the *Journal of the American Medical Association*. 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 publish weekly issues in two volumes each year, with a general index at the end of the second volume. Articles are indexed by both 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 the American Medical Association*. I then read each article to confirm that Darwinism and disease was a central theme.

Figure 1 shows the results for *The British Medical Journal*, and it is clear from the data presented that, in the period between 1881 and 1940, physicians published many reviews, letters, and articles on Darwinism and disease. During this 59 year span, 128 articles were published about Darwinism, whereas between 1941 and 2003, only 67 published articles focused on this topic. Almost all such articles from the latter time period were reviews of books on evolutionary biology, such as the important neo-Darwinian texts of Fisher (1930), Haldane (1949), and Wright (1932). In contrast to this, the works published earlier, between 1881 and 1940, constituted a far more diverse collection of reviews, letters, and articles focused directly on Darwinian interpretation of disease. The peak between

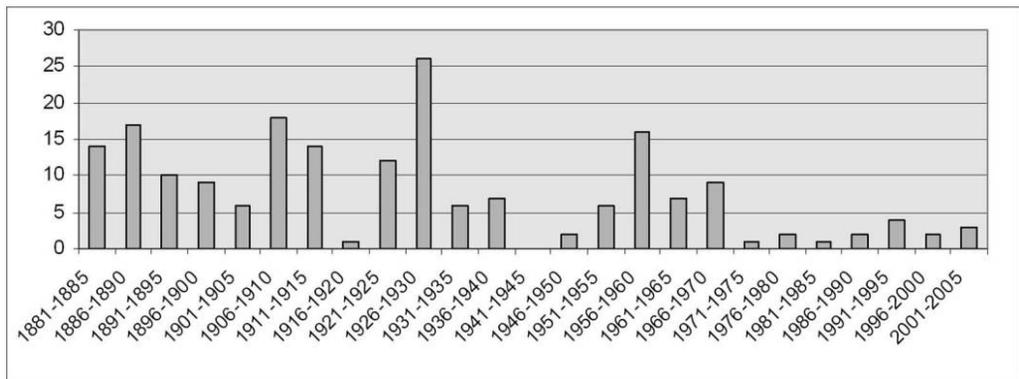


FIGURE 1. NUMBER OF ARTICLES ON DARWINISM IN *BMJ* FOR FIVE YEAR INTERVALS, 1881–2005

Frequency of texts with Darwin, Darwinism, evolution, and/or evolutionism as principal themes featured in *The British Medical Journal* over a 124 year period (Zampieri 2006:253–254).

1951 and 1960 was caused by the 1958 centennial of Darwin and Wallace's presentation of natural selection theory at the Linnean Society, and while the articles published during this peak were not about medical Darwinism, they instead reflected the centennial celebration. The period from 1881–1940 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 celebratory, but some also contained arguments concerning medical Darwinism (Zampieri 2006, 2007). Between 1940 and 1990, 59 articles were published on the topics of Darwin, Darwinism, evolution, and evolutionism. Between 1991, the birth year of Darwinian medicine (Williams and Nesse 1991), and 2003, we find nine articles. If we ignore the peak between 1951 and 1960, for the reasons explained above, we find that, between 1940 and 1990, 43 texts were published, whereas, between 1991 and 2003, there were only nine texts. This amounts to a frequency of 0.71 texts per year in the period between 1940 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 1940 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 that gets more attention in biology than it does in medicine. Also, it is important to note that 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 of the history of two disciplines in countries so different both socially and politically, but here the goal is only to compare and contrast possibly related scientific ideas.

Figure 2 illustrates the results for the *Journal of the American Medical Association* from 1917 to 2003. Over a period of 90 years, only three articles were directly about a Darwinian interpretation of disease: two during the period of medical Darwinism and one during the period of Darwinian medicine. The others were about evolutionary biology, *sensu stricto* (Zampieri 2006, 2007). In 1942, all mention of Darwinism in this journal stopped suddenly, perhaps for obvious reasons. Between 1920 and 1940, George Draper, one of the United States' most important constitutionalists, advocated studying disease by analyzing the human constitution from an evolutionary perspective. This approach was tied to eugenics. Draper and fellow constitution-

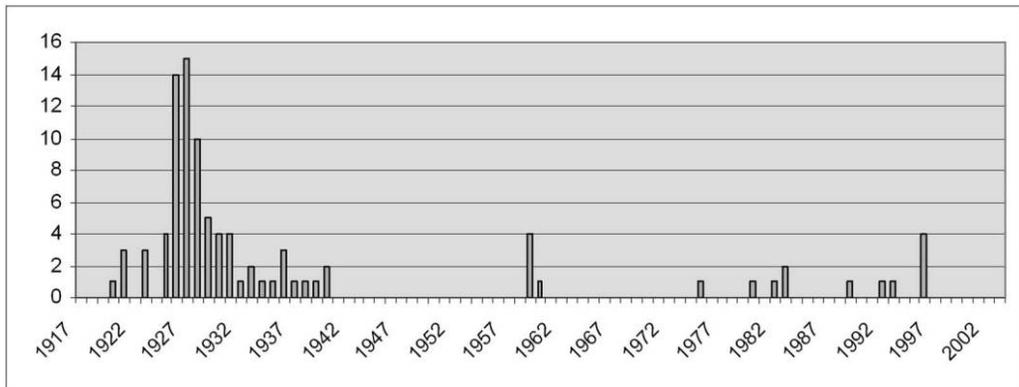


FIGURE 2. NUMBER OF ARTICLES ON DARWINISM IN *JAMA*, 1917–2002

Frequency of texts with Darwin, Darwinism, evolution, and/or evolutionism as principal themes in the *Journal of the American Medical Association* over the course of 85 years (Zampieri 2006:254–255).

alist 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 Davenport, advocated eugenic policies. The horror of Nazi Germany's racially motivated politics caused revulsion in American scientific and public opinion, thus ending American constitutionalism and medical Darwinism (Tracy 1992).

Regarding contemporary Darwinian medicine, it is interesting to compare the system of references of *Evolutionary Origins of Disease*, a text published by English doctor John Harper in 1975 (Harper 1975), with the first monograph on Darwinian medicine, *Why We Get Sick*, published in 1994 by Randolph Nesse and George Williams (Nesse and Williams 1994). A system of references quantifies the frequency and total number of authors quoted in a text, the median value of dates of articles quoted for each author, or a median value for the epoch of an author if he is quoted without referring to a specific text (the median value of the birth and death dates). This can yield insight into how and why a scientist constructs his text, and how and why the text is or is not successful. The comparison between Harper and Nesse & Williams is interesting because Harper, being a precursor temporally near the "dawn" of Darwinian medicine, had little success, and his

texts remained almost unknown, whereas Nesse and Williams, with their monograph and other articles (Williams and Nesse 1991; Nesse and Williams 1994, 1995, 1997, 1999), achieved international success and founded a new discipline. In particular, *Why We Get Sick* was translated into all major world languages, including Chinese and Mandarin, and was *Bild's* (Germany) book of the year for 1994 (Zampieri 2006:228).

Figure 3 shows the authors quoted in Harper's book and Figure 4 the dates of publication of articles quoted (for multiple articles by one author I used a median value), while Figure 5 shows the authors quoted in Nesse and Williams's book, with the relevant dates displayed in Figure 6. Harper's book, at a total of 180 pages, contains 103 quotations, whereas Nesse and Williams's book, at 314 pages, contains 357 quotations; that is, there are 0.57 quotations per page for Harper and 1.13 quotations per page for Nesse and Williams.

This contrast is even more striking because Harper's book was written for doctors and scientists, while Nesse and Williams's book was more popular with a broader audience. However, the contrasting data could indicate that Williams and Nesse, in their time, found more significant literature on Darwinism and disease than Harper. Other data seem to confirm this idea. For instance, the author most quoted in Harper's book is

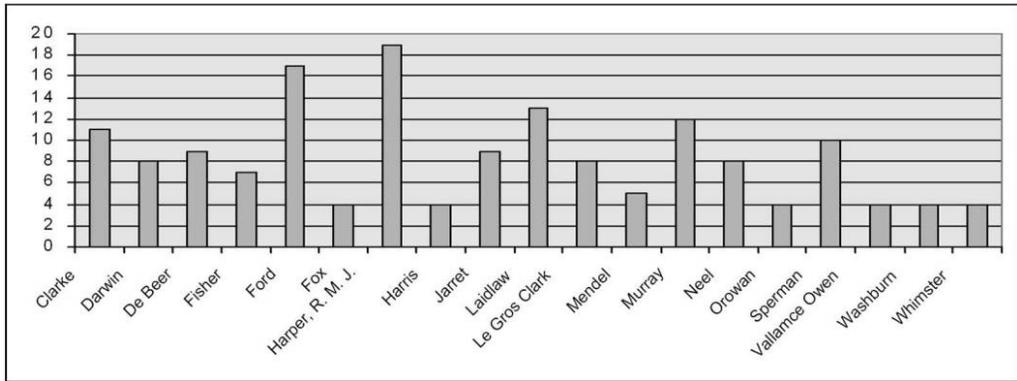


FIGURE 3. AUTHORS QUOTED IN *EVOLUTIONARY ORIGINS OF DISEASE*
 Frequency of authors quoted at least four times in John Harper’s (1975) *Evolutionary Origins of Disease* (Zampieri 2006:195, 261–264).

Harper himself, with 19 references. Second is E. B. Ford (1901–1988), a disciple of Ronald Fisher, quoted principally for the concept of genetic polymorphism (Zampieri 2006:197), and third is George F. Laidlaw (1871–1958), who, in 1932, wrote an article with M. R. Murray on the evolutionary origin of human naevi (Laidlaw and Murray 1932), from which Harper deduced that some pathologies of the human epidermis were reversions to an older structural status (Harper 1975:111–113). The concept of reversion was widely discussed in the old period of medical Darwinism. For example, in medical anthropology, the Italian psychiatrist Cesare Lombroso (1835–1909) explained the nature of criminality and madness as reversions to

states typical of prehistoric humanity (Lombroso 1864, 1876). Reversion and atavism are concepts that find no space in contemporary Darwinian medicine. For the other texts quoted, it is clear that Harper used several sources to find data to confirm his theses, but these texts did not apply Darwinism to medicine. Basically, Harper used his own publications to construct his discourse. This shows again that, in Harper’s time, there was little relevant literature available on Darwinism and medicine; however, this is not to say that such literature was nonexistent. Harper did not quote, for instance, Williams’s article on senescence (Williams 1957), a paper that was crucial for the beginning of the collaboration between Williams and Nesse (Nesse

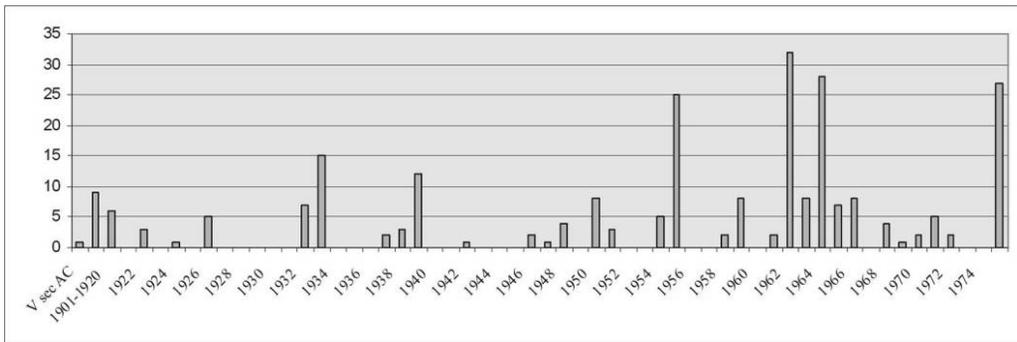


FIGURE 4. MEDIAN VALUE, BY DATE, OF ARTICLES AND AUTHORS CITED IN HARPER’S BOOK
 Immediacy factors of articles and texts quoted by John Harper (1975) in *Evolutionary Origins of Disease* (Zampieri 2006:195).

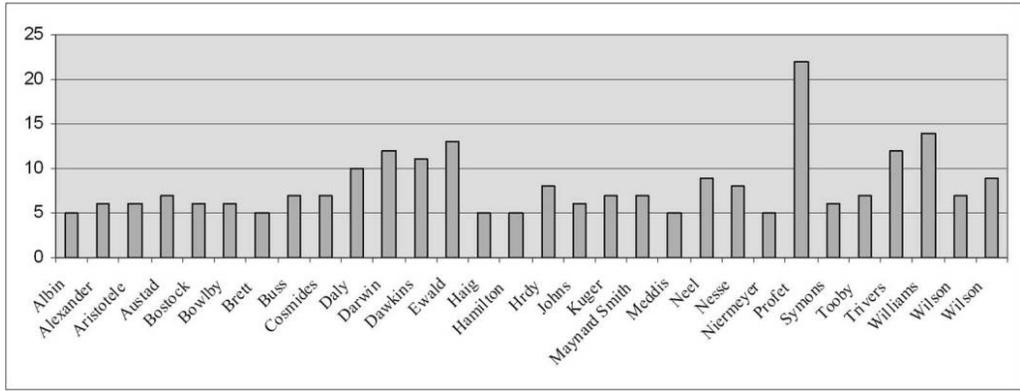


FIGURE 5. AUTHORS QUOTED IN *WHY WE GET SICK*

Frequency of authors quoted at least five times in Nesse and Williams's (1994) *Why We Get Sick* (Zampieri 2006:194, 264–273).

2007). In this article, natural selection, in interaction with pleiotropy, was used to explain senescence. The idea that natural selection works through the reproductive success of genes and not for the health and happiness of individuals is central to contemporary Darwinian or evolutionary medicine. Harper did not show any interest in these texts on natural selection theory (even if he quoted James Neel's theory of "thrifty genotypes" [Neel 1962]), and this was probably why he had a difficult time giving a real evolutionary explanation for why, indeed, we get sick. His explanations did not elicit any reaction in the medical or biological worlds, most

likely because he did not base them in natural selection theory.

The analysis of "immediacy factors" (de Solla Price 1965) gives us some other interesting insights. The immediacy factor represents the tendency of scientists to quote recent publications and to ignore those more than two or three years old. The date that appears most frequently in Harper's book is 1975, the year of publication of the book itself, while the other principal dates are 1963 and 1965—more than ten years before his book's publication. The decade 1930–1940 is also quoted significantly.

Williams and Nesse's book, however, is a

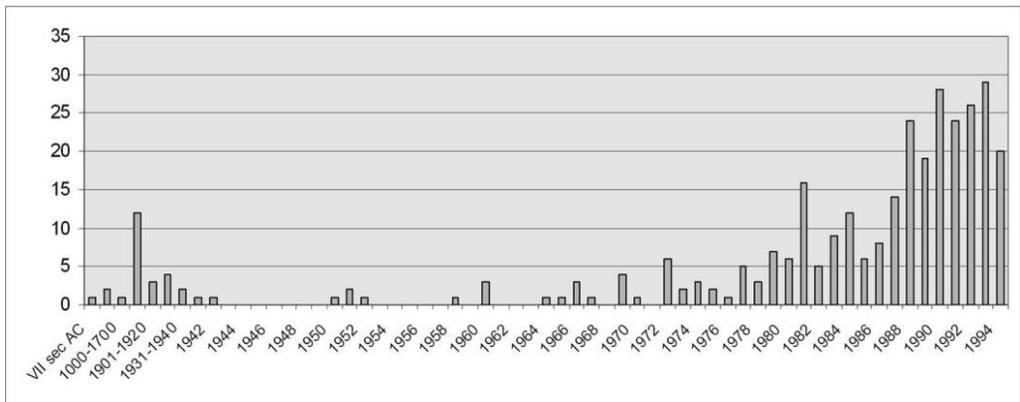


FIGURE 6. MEDIAN VALUE, BY DATE, OF ARTICLES AND AUTHORS CITED IN NESSE & WILLIAMS'S BOOK

Immediacy factors of authors and texts quoted by Nesse and Williams (1994) in *Why We Get Sick* (Zampieri 2006:195).

completely different case. The author most quoted is Margie Profet, an American immunologist whom they considered to be one of the major precursors of Darwinian medicine; Profet wrote a long article on the adaptive function of allergies (Profet 1991). The second most quoted author is Williams himself, given the importance of his theory of senescence for the birth of Darwinian medicine, followed third by E. O. Wilson, founder of contemporary sociobiology. Also important is the fourth most quoted author, Paul Ewald, who studied the evolution of infectious diseases, focusing on the selective mechanisms that shape coevolution between host and parasite (Ewald 1980, 1993, 1994). Ewald and Profet, in the acknowledgments at the beginning of Williams and Nesse's book, are defined as "pioneers" of the new discipline (1994:vi). Many other significant texts on Darwinism and medicine are quoted by Williams and Nesse, such as *Human Adaptation* (Harrison 1993) and *The Anthropology of Disease* (Harrison 1994). This illustrates that Williams and Nesse were clearly able to find relevant literature on the topic of evolution and disease—a topic that started to flourish in the 1980s. Analysis of the immediacy factor confirms this hypothesis. The most frequent date of articles quoted is 1993—just one year before Williams and Nesse's book—followed by 1990. Almost all citations are from 1988 to 1994.

Based on this preliminary analysis, it seems that Williams and Nesse founded Darwinian medicine because they found themselves in the right place at the right time. They had the great merit of bringing together many previously unrelated new insights on the evolution of disease in a vision focused principally on the Darwinian mechanism of natural selection, as modified by advances in evolutionary biology from the second half of the 20th century. Just a couple years after the publication of the very first article on Darwinian medicine in 1991, several authors published along the lines indicated by Williams and Nesse. The reaction was immediate. The subsequent development of this new discipline offered an increasingly complex picture in which ever more scientists began to recognize each

other as protagonists of a new scientific revolution.

In the next two sections, I will examine in greater detail the major concepts of the old medical Darwinism and current Darwinian or evolutionary medicine, and I will demonstrate that the latter truly seems to be a new addition to the scientific panorama.

MEDICAL DARWINISM: 1880–1940

The work of Erasmus Darwin, grandfather of Charles, was the major precursor of medical Darwinism, but the question of evolution of disease remained unexplored until the publication of the younger Darwin's *On the Origin of Species* (1859). In the writings of Charles Darwin, 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. As an anonymous reviewer of Darwin's time noted, "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" (Editorial 1888:380). In Darwin's early notebooks, many observations are tied to his father's medical practice (Bynum 1983). For instance, in *The Variation of Animals and Plants under Domestication* (Darwin 1875) we find, in Chapter XII, many examples of hereditary diseases in humans, animals, and vegetables as proof of inheritance of variation (for a wider analysis of Darwin, see: Bynum 1983; Corbellini 1998; Zampieri 2006, 2007).

Classical Darwinism (1860–1920) asserted that evolution was a selective process based on heredity and variation, a process through which "types" were shaped: groups of organisms with some fundamental structural, functional, and behavioral characteristics in common, resulting from natural selection that eliminated unfavorable variations and accumulated favorable variations for survival and reproduction of individuals and groups. "Types" could be species, variet-

ies, races, or families, according to the extension given each time to this basic idea. In this sense, classical Darwinism had in part a typological approach, in which the aim was to discover how evolution had shaped—or rather, had modified—organic types that were more or less fixed (Mayr 1983). Humans being the principal object of medicine, the application of Darwinism to the health sciences started with the study of the heredity of diseases and its action in the formation of human types, such as races and families. Concepts like temperament, diathesis, and constitution interlaced at the centre of a great transnational research program that involved several biological and medical disciplines, including the clinic, anthropometry, microbiology, immunology, neurology, psychology and psychiatry, genetics, and physiology (Bynum 1983; Tracy 1992; Burgio 1995; Grmek 1995; Zampieri 2007). In this way, medical Darwinism helped bring an end to a research program that had accompanied medicine from its historical beginnings.

For more than two millennia, medical theory focused on the construction and elaboration of categories of patient constitutions useful for the practice of medicine. The individual differences in health and disease were set up in a system in which there were fundamental types of humans, each with typical characteristics and predispositions to health and disease. Classical medicine was founded on the theory of humors (humoralism: see Glossary), which, in turn, was structured on the system of temperaments. Human diversity was related to variation based on four themes or types, each characterized by precise structural, functional, and psychological characteristics. Each temperament—sanguine, phlegmatic, melancholic, and choleric—was the result of the prevalence of one of the four humors: blood, phlegm (a sort of mucus that originated from the brain), black bile (spleen), and yellow bile (liver) respectively. The appeal of this structure was evident, as it provided a unitary concept of disease and a system of universal care, applicable in every individual case. This theory was still alive in the 17th century, almost two thousand years after its foundation, but soon thereafter it was

eclipsed by the new pathological anatomy codified by Giambattista Morgagni (1682–1771), whose basic idea was that all disease depended not on a humoral disequilibrium, but on a specific organic lesion (solidism: see Glossary). Despite the enormous success of this new approach, the older system of temperament survived with a new theoretical foundation. The four temperaments were now based on the prevalence of an organ or apparatus instead of a humor: heart and circulatory system for the sanguine, lymphatic system for the phlegmatic (which was renamed “lymphatic”), digestive system and liver for the melancholic (which was renamed “bilious”), and nervous system for the choleric (which was renamed “nervous”). This theoretical structure held until the second part of the 19th century, supported in its last period by the phrenological school (Jacques 1878), but it could not resist the rise of experimental medicine.

Although the term “temperament” disappeared, the basic idea did not die; on the contrary, it re-emerged forcefully in the concept of diathesis and in the constitutional school between 1880 and 1940 (see Glossary). But now, to support both these approaches, instead of a vague philosophical theory or an intuitive idea (even if defensible—that is, humanity could be divided into different, more or less stable, varieties), there was the Darwinian theory of evolution, thanks to which it was possible to wrap both approaches within the indispensable scientific aura. In this way, toward the 1880s, there emerged a theory of universal diatheses, promulgated initially by the English clinician Jonathan Hutchinson (1828–1913), and then widely spread among doctors (Hutchinson 1884; Douglas Lithgow 1889; De Giovanni 1891; Garrod 1909, 1927; Lery 1912). The concept of diathesis had existed since Hippocrates, but only in this period did it become widely influential, exactly because it filled the gap left by the death of temperaments (Ackerknecht 1982). A diathesis was an individual disposition, hereditary or acquired, to an ensemble of pathologies with common characteristics. Universal diatheses were: tuberculous (predisposition to tubercular diseases and, generally, to every neo-

plastic growth), rheumatic (predisposition to muscle-skeletal inflammation), and nervous (predisposition to nervous disorders). Each of these evoked one or more temperaments, in a charming continuity not yet fully appreciated by historical analysis. This system was founded in Darwinian terms because diatheses were considered to be products of Darwinian evolution. Each diathesis had emerged in parallel with the evolution of one or more fundamental organic structures: tuberculous was related to the vascular, lymphatic, and digestive systems (bilious and lymphatic temperament); rheumatic to the muscle-skeletal system (sanguine temperament); and nervous, obviously, to the nervous system (choleric temperament). Even though evolution was thought to have built these structures in a perfect way, they could vary generation by generation, causing vulnerabilities that were then also configured in diatheses.

Diatheses were individual characteristics, the boundaries of which were not clear. Each individual could present a predominant diathesis, mixed with characteristics of other diatheses. For example, a person could be tuberculous but also have some rheumatic derangements. Before Darwinism, the majority of doctors in England shared Hunter's theory on the impossibility of mixed diseases (John Hunter, 1728–1793, a Scottish surgeon regarded as one of the most distinguished scientists and surgeons of his day). According to this theory, an individual could have two or more diseases at the same time, but not in the same part of the body. Hunter rejected explicitly the idea of rheumatic-gout, for example. Thanks to Darwinism, doctors could interpret rheumatic-gout as a mixed disease received through heredity (for example, the result of a gouty father and rheumatic mother), or as an eventually hereditary modification of one of these diseases (a rheumatic father gives rise to a gouty-rheumatic child).

Toward the end of the 19th century, the diathesis concept faded (Ackerknecht 1982; Burgio 1995; Brown 2001; Waller 2002), for several reasons. While in part caused by external factors, including progress in medical

science in discovering specific causes of diseases previously considered to be diathetic (e.g., tuberculosis [see Brown 2001]), the main internal problems arose from the decline of Darwinism between the end of the 19th and the beginning of the 20th century (Huxley 1942) and the simultaneous decline of some hereditary theories (i.e., blending heredity, development of a tendency through heredity, heredity of acquired characters). In some sense, in conceptualizing diatheses, heredity was used as a *deus ex machina*—a concept used to explain something that otherwise could not be explained (Campbell 1889; Waller 2002)—and this was the major shortcoming criticized by its opponents.

Still, diathesis theory did not die out completely. It was reabsorbed by constitutionalism, an approach that was born in Germany and Italy at the beginning of the 19th century and that, until the Second World War, propelled a major research program that gave rise to a long series of discoveries in a great variety of biological and medical disciplines, but which, at the same time, was involved in turbid eugenic and racial questions (Porter 1996). Authors who discussed 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, they sometimes treated diathesis and constitution as synonymous (Quain 1882; Editorial 1927a; Anonymous 1931, 1932). Until the 1910s, constitutionalism was still based mostly on a Lamarckian perspective, given the importance attributed to the heredity of acquired characters (De Giovanni 1891, 1904; Adami 1907), but, after the formation of neo-Darwinism, this system of thought adopted a Mendelian theory of heredity (see Draper 1925).

The most famous constitutional system was that of German psychiatrist Erns Kretschmer (1888–1964), which proposed three fundamental constitutions: the *athletic type* (solid osseous constitution, great development of muscular mass, disposed to hypertension, hyperglycaemia, schizoid disorders), the *asthenic type* (normal long-limbed development, but insufficient in breadth, hyposupra-

renal, disposed to schizoid disorders), and the *picnic type* (panniculus adiposus developed on the trunk and abdomen, stocky, disposed to a suprarenal hyperfunction and to manic-depressive disorders) (Kretschmer 1925). Again, the correspondence of this system with temperaments and diatheses is amazing. Each constitution had an adaptive side and a set of specific pathological dispositions. The contribution of the Darwinian paradigm was to conceive of adaptive characters—generally, we can say physical and intellectual force for athletic, intelligence and elasticity for asthenic, resistance and obstinacy for picnic—as products of natural selection, and the pathologies as deviations, hereditary or heritable, due to the natural variability of organisms. It is important to note that in constitutionalism, the evolutionary perspective was important, but not fundamental. The idea that constitutions were evolutionary products was an accessory whose function was to give a biological foundation to the theory, but the focus of research into constitution remained limited to the determination of actual features of constitutional types.

The research into what determines the fundamental constitutions of humans was carried out with several methods and gave rise to new research programs. One approach tried to determine structural norms by anthropometric measurements and statistical analysis, while another tried to determine functional norms by analyzing the biochemical composition of blood, urine, gastric secretions, metabolism, and endocrine functions, and by also analyzing psychological and immunological sensibility and reactivity. The current routine clinical examinations (blood and urine, for instance) are still based on these studies, which originated between the end of the 19th century and the beginning of the 20th century.

The theory of universal diatheses and the constitutional schools were also related to microbiology and the debate about the priority of seeds or soil in the emergence of infectious disease. At the time of the 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, most of whom were British, tried to employ Darwin's theory of evolution to react against the power of the germ theory paradigm, for the issue was seen as a battle between national heroes, Darwin and Pasteur, representing two nations that had a poor relationship (experimental physiology had also produced irrational resistance in England because of its French tradition, and Darwin met with some resistance in France just because he was British [Bynum 1983]). It is important to note, however, that Pasteur and Darwin never met, and there was no apparent rivalry between them (Bynum 1983). Darwinian doctors reacted 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 proof that the concept of specificity of infectious disease—one species of germs equals one specific infectious disease—lacked biological basis. Darwinian doctors believed that a germ could evolve from one species to another in the course of a single infection. Hutchinson also denied the necessity of germs for infectious disease, for an infection could be caused by individual diathesis (Hutchinson 1884). For microbiologists, the external cause of an infectious disease—the germ—was seen as much more important. Doctors who followed medical Darwinism considered germs just as important as internal causes; that is, the individual reaction as determined by hereditary constitution. According to K. M. Millican, who published *Evolution of Morbid Germs* in 1883, 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 (Ait-

ken 1885). Furthermore, for the English physician J. D. Adami, and for other physicians at the end of the 19th century, the evolution of bacteria was proof of the heredity of acquired characters. Bacteria evolved from a nonvirulent to a virulent form via direct action of the environment on microorganisms, which then passed on this modification by heredity (Adami 1918). Also, the conception of heritable 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* (1890), 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 necessarily imply that species do not exist. The definitive reconciliation between Darwinism and microbiology most likely came with the French bacteriologist Charles-Jules-Henry Nicolle (1866–1936). According to Nicolle, microorganisms evolved in the same way as other natural populations, and his findings refuted the idea that one bacterial species could change into another in the course of an infection (Nicolle 1930, 1933).

The theory of universal diatheses and the constitutional school were also related to the concept of diseases of civilization. In the first part of the 19th century, it was common opinion that diseases of civilization depended only on environment. After the birth of Darwinism, the model was increasingly expanded to also consider heredity (Bynum 1983; Porter 1993). The concept of hereditary degeneration became the key to understanding the multitude of maladapted and sick individuals that the new industrial society presented and 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:xc). In the 1866 edition, the former paragraph on

degeneration became an entire chapter in which Aitken also discussed the mental and moral degeneration of the poor (Aitken 1866:132–148). For medical Darwinism, diseases of civilization were proof that natural selection did not 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 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 does not 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” (1983:47). This misconception resulted from thinking of natural selection as eliminating through mortality, rather than changing through differential reproductive success. In fact, modern medicine has not eliminated natural selection, for there is still plenty of individual variation in reproductive success in modern human populations. It has, however, changed the traits on which natural selection is acting most strongly, and we do not yet know precisely which traits have been most affected. Research on this topic has now begun.

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 detailed discussion of which is beyond the scope of this article. Briefly, diathetic and constitutional disorders were considered characteristics of the civilized elite, and included maladies such as hysteria, gout, and hypochondria, whereas primitive people and the industrial poor were thought to succumb primarily to acute epidemic diseases (Bynum 1983), with some diathetic and constitutional diseases of the poor of secondary importance, such as alcoholic diathesis. The British neurologist John Hughlings Jackson (1835–1911) observed that, in alcoholic diathesis, the progressive degeneration of brain functions followed, in

reverse order, the evolutionary route of formation of different brain areas. The first to degenerate was the area for judgment and memory, then the area for language and emotions, and finally the vegetative area for respiration and circulation (Jackson 1887). This idea appears to have been inspired by Haeckel's dictum: ontogeny recapitulates phylogeny, alcoholic degeneration being a sort of recapitulation in reverse.

To improve the human species and to counter the failure of natural selection in the civilized world, the proposed solution was a program of eugenics. Eugenic ideas were promoted for decades before Francis Galton named the field in 1883 (Kevles 1985). Its aim was to prevent the increase of disorders attributed to hereditary characteristics, such as insanity, alcoholism, and prostitution. These characteristics were prevalent among the industrial poor, so they, consequently, bore the brunt of eugenic measures. For civilized elites, on the contrary, diathetic and constitutional 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).

Toward the middle of the 20th century, the theoretical adventure concerning temperaments, diatheses, and constitutions that started more than two millennia before, declined in the face of a new medicine that was divided into specialties. Each discipline was by now so specific and so full of concepts and methods that it was technically impossible to support a holistic approach. The decline of Darwinism in medicine, moreover, coincided with the Flexner reform, which focused most medical research on experimentation (Lawrence 1993; Corbellini 2002). In 1922, the British 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 had probably offended the cognitive medical preference for monocausal explanations (Nesse 2005). There were also religious issues, for, in the first decades of the 20th century, the teaching of Darwinism was forbidden in several US states: in 1926 in Mississippi and North Carolina (*JAMA* 1926a:960, 1926b:1704) and in 1928 in Kentucky (*JAMA* 1928:751), with attempted bans in Florida and Arkansas in 1927 (*JAMA* 1927b:1423, 1927c:653). Even today, battles continue that limit the teaching of evolution in the USA, even if they do not prohibit it. And, as noted above, constitutionalism and medical Darwinism also subsided because they were related to eugenic and racial typology. When doctors talked about constitution, they soon substituted the term “race” for “constitution.” The idea that some races were better than or superior to others seemed to have a biological, medical, and Darwinian justification. Concepts such as atavism and degeneration were leitmotifs of racial typology in medicine, sociology, and politics (Lombroso 1864, 1876; Ackerknecht 1957; Kevles 1985). Constitutionalism declined after the Second World War, mostly as a consequence of its relationship with Nazi ideology, for constitutional concepts had been used to justify a racial typology of men. These general comments merit further research.

In the period of medical Darwinism (1880–1940), we can find several, sometimes very different, medical Darwinian schools and evolutionary theories of disease, and although both Darwinism and medicine changed profoundly during those sixty years, I believe that there was a common thread running through the various manifestations that came into being during that time.

The most striking characteristic of medical Darwinism was its *typological* approach. Ernst Mayr suggested that the most important revolution of Darwinism was the substitution of the *populational* approach for the *typological* approach in the study of species (Mayr 1983: 17). The typological approach derived from Platonic philosophy, according to which a limited number of fixed and immutable “ideas” were at the base of variability in na-

ture. Discontinuities among these ideal templates explained intervals in nature—that is, the differences between species. In contrast, the population approach is based on the uniqueness of every individual in the organic world. Every organism has unique characteristics, and populations of organisms can be described only in statistical terms, where statistical averages are abstractions and populations are conceptualized, not in terms of mean values, but as frequency distributions.

At least in the medical sciences, Darwinism remained curiously mixed with a typological approach long after the publication of *On the Origin of Species* (Darwin 1859). The concept of variation had no value in itself, rather only in relation to a norm or a type. The theory of universal diatheses presented diatheses as fundamental constitutional typologies present in all humans in pure or mixed form. Individuality was nothing more than an inconsequential variation of these pure forms. Moreover, diagnosis and therapy were conducted by referring to universal diatheses rather than to individuals. The statistical approach, so important in population thinking, was also used by constitutional physicians, but without a full awareness of the nature of statistics. Constitutionalist tried to always find the ideal type of constitution, or the norm to which all variation could be referred. Here, the relationship with the old theory of temperaments was even more pronounced than in diatheses. Both approaches, in fact, had a tendency to present the type as an ideal picture, designed by doctors themselves, with all typical characteristics and proportions. Constitutionalist also used photographs of patients, all to the same purpose: to show an ideal type. This was due, most likely, to the persistence of the tendency, throughout the entire history of medicine, to try to find an ideal healthy type of human. This ideal could give fundamental insight into disease, which was considered to be a degeneration of the original type, and a general structure for therapy, whose aim was necessarily to restore each degeneration to the ideal type. Temperaments, diatheses, and constitutions are the historical manifestations of this medical “philosopher’s stone.”

Darwinism was inserted into this structure, but the result was a failure.

From this perspective, evolution was seen principally as a process by which fundamental diatheses or constitutions could vary or mix together generation by generation, or as the process by which constitutions were shaped back in the remote past when the human species was formed. Despite this acknowledgment of some potential dynamics, constitutions were seen as ideal structures, ultimately unchangeable. Based on this structure, natural selection was necessarily a process of all or nothing. According to typological thinking, each thing in nature was good or bad, useful or harmful. Natural selection enabled the conservation of higher types and the rejection of lower types (Mayr 1983:20). This way of thinking fit classical medicine particularly well, for it resonated with a conception of health and disease as two entities separate and incompatible.

The second most striking characteristic of medical Darwinism was the justification of the persistence of pathological characteristics as traits that had escaped elimination by natural selection. Given that pathologies were negative traits, it was natural to think that they ought to have been eliminated by natural selection. The fact of their persistence in the heredity and natural history of humans was necessarily proof that these characteristics could escape selective elimination. The most common justification for this was, firstly, based on the spontaneity of organic variability. In each generation new variations arose, some useful and others harmful. Thus, if natural selection eliminated harmful variations in one generation, they would emerge again in the offspring of following generations (Paget 1883; Garrod 1927). Secondly, the typical justification for humans was that natural selection no longer worked properly in the case of civilized humans, and medical care was thought to be one of the main factors responsible for this situation. Medicine keeps alive many who would otherwise have perished, allowing them to reproduce their negative, degenerative, and hereditary characteristics (Tait 1869; Lindsay 1909).

The typological approach and the concept

of selection as a process of all or nothing were the main features of medical Darwinism that could not survive the progress in Darwinism studies that accelerated during the second half of the 20th century, giving rise to current Darwinian medicine.

DARWINIAN MEDICINE: 1991–2009

“Darwinian medicine,” as it is currently defined, first appeared in 1991 in an article by George Williams and Randolph Nesse, entitled “The dawn of Darwinian medicine,” published in *The Quarterly Review of Biology* (Williams and Nesse 1991) (the term “Darwinian medicine” was actually used for the very first time by Dr. Benjamin Ward Richardson [1828–1896] in an article published in 1893 [Richardson 1893], but he was speaking about the medicine of Erasmus Darwin, without any suggestion of a new discipline). In Darwinian medicine, the population approach is fully applied in conceptualizing human pathology. This became possible because of several advances and discoveries that clarified the basic concepts of evolutionary biology. The first was that natural selection works principally at the level of genes, not that of individuals or species (Fisher 1930; Williams 1966). This approach allowed us to understand that natural selection cannot make a perfect machine and that it does not shape the health and happiness of individuals or a species, for it works only on the reproductive success of genes. This was also the first step to understanding the problems of altruism, sexual selection, and senescence (Williams 1957; Hamilton 1964; Wilson 1975; Cronin 1991). The discovery of genetic polymorphism was fundamental, for it gave a quantitative basis to the uniqueness of each individual and established the usually extensive variation that exists within each population (Lewontin and Hubby 1966a,b; Lewontin 1974). Moreover, the study of polymorphism let us see more clearly that natural selection works at different levels and that there are other complementary mechanisms that also maintain variability. Another important advance came from the concept of genetic pleiotropy, which led to our understanding that some genes can have different effects, both positive and negative (Haldane 1949). This

permitted the formulation of a theory of senescence based on the natural selection of genes (Williams 1957), a shared interest that helped Nesse and Williams start their collaboration, and the topic around which the first ideas of Darwinian medicine developed. The phenotypic analogue of pleiotropy—trade-offs among traits—is one of the most important explanations of vulnerability to disease. A trade-off exists when an evolutionary improvement in the contribution to fitness of one trait is linked through development and physiology to an erosion in the contribution to fitness of another trait. Such connections among traits are caused both by pleiotropy and by genetic linkage.

Darwinian medicine also emphasizes the role of natural selection in shaping and maintaining adaptations (Williams 1966). Far from perfect, adaptations are always imperfect compromises because they are the products of natural selection. The work of natural selection is not absolute; it is a *bricolage* (Jacob 1970). The most accurate definition of natural selection, in my opinion, appears in an article by Stearns and Ebert: “Natural selection on a trait is the correlation between variation in the trait and variation in reproductive success” (2001:427). This definition is rooted in Robertson’s (1966) Secondary Theorem of Natural Selection, generalized by Price (1970) in his famous equation, and developed into an applicable method by Lande and Arnold (1983) in one of the most cited papers in evolutionary quantitative genetics. At its root, natural selection is the consequence of the differential reproduction of genes. And here we may have the ultimate explanation of individual vulnerability. Genes become more frequent if they create bodies that reproduce more than others. Such individuals tend to be healthy, but a gene that increases reproduction at the expense of health will nonetheless tend to become more prevalent. Like traits, alleles have costs and benefits, one cost being a vulnerability to one or more pathologies.

In addition, focusing only on adaptation and disease can be misleading, for the concept of adaptation is itself problematic in

several ways. The concept seems to imply that adaptations correspond to machinery that is well-designed and useful for the individual. In reality, perfect adaptations do not exist in the biological world, for all traits are compromises on some level. In fact, one may just as well speak about *maladaptations*, for every trait that can be defined as an adaptation has some aspects that are functional and others that are useless or even harmful to individuals. Nesse, in a playful reference to the title of Williams's 1966 book, wrote of "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 in the reproductive success of genes in bodies interacting with environments. If we consider adaptation as a trait produced by evolution and based on the reproductive success of genes, the phenotypic outcome must almost always be a compromise, for the reproductive success of genes is not directly connected to the health, happiness, and functionality of individuals. The best examples of this are genes that increase fecundity while compromising survival, such as those responsible for senescence (Williams 1957).

Between 1960 and 1990, precursors of Darwinian medicine appeared in several fields. The English physician John Harper, mentioned above, published many studies on the evolutionary interpretation of disease between 1960 and 1970 (e.g., Harper 1975), while René Dubos worked on the relative concepts of health and disease (Dubos 1965). Ewald (1980) discussed the evolutionary interpretation of infectious diseases, Margie Profet (1991) advanced an evolutionary theory of allergies, David Haig (1993) applied the theory of kin selection and parent-offspring conflict to pregnancy and other issues in reproductive medicine, and Boyd Eaton (1990; Eaton et al. 1988) was a pioneer in evolutionary medical anthropology.

Some evolutionary insights and methods were used in medicine long before the advent of Darwinian medicine; they include human population genetics, the study of antibiotic resistance, and the techniques used to trace the phylogenies of viruses and bac-

teria. Darwinian medicine has surely profited from these methodologies, but it goes beyond them in its questions and research. In fact, it also asks questions about adaptation, and these questions need answers that are not only quantitative. Darwinian medicine uses a wide range of methodologies, from genetics to comparative anatomy, for testing hypotheses about adaptation, but what is really new for medicine is the set of starting questions. Questioning the adaptive value of traits that leave us vulnerable to disease is, historically, a new question and leads to new research programs and, possibly, to new answers.

The nature, structure, and purpose of Darwinian medicine is not just empirical; it depends also on epistemological decisions made by its authors. It is not by chance that the question of nomenclature is still open. Among the major monographs on the topic, only that of Nesse and Williams uses the term "Darwinian medicine." McGuire and Troisi write along the same lines using "Darwinian psychiatry," while still others speak about "evolutionary medicine," "evolution and healing," or "evolution of infectious disease" (Williams and Nesse 1991; Ewald 1993; Nesse and Williams 1994; McGuire and Troisi 1998; Stearns 1999; Trevathan et al. 1999, 2007; Trevathan 2007; Stearns and Koella 2008). The choice to use the term "Darwinian" is not only tied to the risk implied in its pejorative connotation, but also to a profound perception of the nature of this new discipline. Nesse advocated that "Darwinian medicine" is more precise because it refers directly to the theory of natural selection (Nesse 2007). Some authors prefer to use "evolutionary medicine" or other similar terms because evolutionary biology is more than natural selection theory. Other authors, as mentioned by Nesse himself, do not think it useful to use either "Darwinian medicine" or "evolutionary medicine," as this may risk suggesting a separate and independent field of medicine (Nesse 2007), despite the fact that this discipline aims to be a basic science for all medicine (Nesse et al. 2006).

As a debate around nomenclature can be quite sterile, I think it important to

establish the core concepts around which Darwinian medicine organizes its program. Evolutionary concepts of relevance to the health sciences are: natural selection, genetic drift, adaptation, coevolution, host-parasite arms race, defense and the “smoke detector principle,” traits balanced between costs and benefits via trade-offs, genetic quirks, reproductive advantage at the expense of individual maintenance and survival, constraints, evolutionary legacy, and mismatches to the modern environment (Williams and Nesse 1991; Ewald 1993; Nesse and Williams 1994; McGuire and Troisi 1998; Stearns 1999; Trevathan et al. 1999, 2007; Stearns and Koella 2008). In the major texts of the new discipline, we find theories about the evolutionary origin of vulnerability to cancer, virulence, allergies, and sexual and mental disorders, as well as neonatal, childhood, or puberty disorders and chronic degenerative diseases. We find detailed explications of breast cancer, HIV, child abuse, substance abuse, schizophrenia, depression, childhood asthma, coronary heart disease, hypertension, diabetes, and obesity. There is also some discussion of conditions not directly pathological, but of clinical relevance, such as menopause and senescence. We find discussions of normal capacities that lead to disease when then go awry, such as anxiety, pain, sadness, and guilt. Finally, topics related to epidemiology are also addressed, such as genetic geography and public health policy about drugs, infectious diseases, and vaccines. The catalogue would be wider and more complex if we took into consideration not only the texts quoted above, but the entire body of literature on Darwinian medicine produced since the discipline was founded.

Nesse and Stearns proposed a scheme for the categories of evolutionary questions and objects of explanation (2008:32). There are two kinds of evolutionary questions—one related to phylogeny (history and relationship), and the other related to adaptive significance (selection and drift). Each of these can be applied to one of five kinds of objects of explanation: human traits, human

genes, pathogen traits, pathogen genes, and cell lines.

Evolutionary explanations of disease can be ordered into several categories. First, the main distinction is between disease and disease vulnerability (I discuss the population concept of vulnerability below). According to Williams and Nesse, the Darwinian approach can be useful only if applied to vulnerability rather than to disease itself because, setting aside some exceptions, natural selection does not shape disease. Natural selection shapes structures and functions that, being imperfect, are vulnerable to dysfunction or disease. This does not mean, however, that evolutionary medicine has worked only with this perspective.

Nesse and Williams (1994) proposed “six reasons for disease vulnerability” (Nesse 2005: 66–68) that are all related to how natural selection works: 1) the response to natural selection can be slow relative to the rate of environmental change, causing a mismatch between design and environment; 2) natural selection can be slower in the host than in the pathogen, this being crucial especially in competition with a pathogen that reproduces more quickly than humans; 3) selection cannot solve some problems no matter how much time it is given, for tradeoffs force compromises; 4) natural selection cannot solve some problems irrespective of time, for there are constraints peculiar to living systems, e.g., path-dependence (here we find the importance of constraints of development treated by the evo-devo approach: see Gerhart and Kirschner 1997; Minelli 2003); 5) we misunderstand what selection shapes, not seeing traits that increase reproductive success at the cost of disease vulnerability; and 6) we may misunderstand what selection shapes, as defenses can be readily mistaken for diseases.

Stearns and Ebert, in an article that reviewed the progress of Darwinian medicine during the ten years from 1991 to 2001, proposed a wider list of evolutionary explanations for disease, based on two fundamental ideas: 1) *human nature*, related to its evolutionary past, its phenotypes and characters with costs, benefits, and constraints, evolved under different conditions or

adapted principally in the Stone Age (this is another way of expressing maladaptations to modernity or diseases of civilization—another way of expressing an old explanation); and 2) *genetic conflicts*, which confer on genes and characters dynamics that can be expressed as pathologies (Stearns and Ebert 2001:420–421).

We believe that Williams and Nesse's focus on vulnerability, rather than disease, is the most significant conceptual characteristic of Darwinian or evolutionary medicine. This concept always appears in discussions of the theoretical foundation of the discipline (Nesse and Williams 1994; Nesse 2005; Nesse et al. 2006; Nesse and Stearns 2008). The idea is that evolution does not shape disease, but only the anatomical, physiological, and psychological characters that can be vulnerable to disease. Most such characters are vulnerable because natural selection shapes optimal compromises, not perfection.

Vulnerability to disease can represent the expression, cost, defective aspect, limit, or mismatch between old and new environments of an adaptation (Zampieri 2009b). Natural selection helps to produce vulnerability, for, on the one hand, its essence is the correlation between variation in a trait and variation in reproductive success, while, on the other hand, it is a mechanism that can act simultaneously on different levels (genes, phenotypes, kin, populations, species) in concert with other evolutionary mechanisms, including genetic drift and developmental constraints (Stearns 1999). Because natural selection works through the differential reproductive success of genes, it must work on levels that sometimes oppose each other (e.g., genes vs. individuals or individual vs. species), and, because it is constrained by history, development, physics, and chemistry, the traits and vulnerabilities that it produces are imperfect.

In current Darwinian or evolutionary medicine, vulnerability is a population concept. It studies the vulnerabilities of the human species as a whole to specific dysfunctions or disorders. The example of bipedalism is the clearest and most common; all humans, being bipeds, are

vulnerable to pain and disorders of the dorsal spine. In Darwinian medicine, each disease is related to an evolutionary vulnerability explained by historical origin, genetic and developmental mechanism, and/or coevolutionary history with a pathogen. If we have a noninfectious disease, the main hypothesis is: which kind of evolutionary vulnerability is implied? This hypothesis can be tested by finding an historical origin—that is, asserting that this disease is the byproduct of a specific human gene character or behavior. The hypothesis can also be tested with genetic analysis, in terms of direct or indirect causation (Childs 1999). If it is indirect, the genetic involvement is in terms of determining the susceptibility or predisposition of a specific developmental trait or behavior. If the disease is infectious, we also have to add a history of coevolution between host and pathogen, both in terms of coevolution through several generations of host and pathogen, and in terms of coevolution between an individual host and several generations of a given pathogen in a single infection. This type of general species-specific vulnerability is considered an abstraction only useful to determine some points of reference, for it represents a general characteristic of frequency distribution. The reality is that the individual variation and the uniqueness of individual vulnerability is determined by a unique genome and phenotype. Individual variability is also better seen in patterns among populations, rather than among species. The case of sickle cell anemia is paradigmatic: populations that live where malaria is endemic are selected with a balanced polymorphism at a locus that results in sickle cell anemia in homozygous conditions, but in protection against malaria in heterozygous conditions (Haldane 1949). The population thinking intrinsic to a Darwinian approach emphasizes that it is a mistake to think that there is one version of a trait that is considered "normal." Traits are characterized by a spectrum of possible variations or alternatives and by a specific frequency distribution. Moreover, individual variability is not determined by genes; it is plasticity arising from interactions between genes and en-

vironments. 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.

The arrival of this population approach to medicine was probably favored both by the development of evolutionary medicine and by the relative concepts of health and disease that were imposed upon medicine in the second half of the 20th century. Psychiatry, at the beginning of the 20th century, began to see disease as a social construction rather than as an ontological phenomenon, proposing the idea that there exists neither a pure disease nor a pure state of health. This concept was fully developed in the last part of the century by the philosophy of medicine and by psychiatry itself (see, for instance, the work of Michel Foucault and 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 contribution 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.

As one can see, the main types of problems in medical Darwinism and in Darwinian medicine have been almost the same. In medical Darwinism, diathesis and constitution were the basic concepts for understanding the question of pathological predisposition, heredity, and development, while in Darwinian medicine, these problems are principally discussed within the concept of vulnerability. However, Darwinian medicine does not try to find evolutionary explanations for fundamental constitutions, as did the old medical Darwinism, precisely because it has adopted a population approach. Diseases of civilization are an important concept in medical Darwinism, favored by the development of the anthropological sciences between the end of the 19th century and the beginning of the 20th century, and mostly related to the debate on the effective-

ness of natural selection on civilized populations. Darwinian medicine uses a broad anthropological approach to determine the origins of diseases of civilization (Trevathan 2007; Trevathan et al. 1999, 2007), but it never speaks of degeneration, nor does it propose that natural selection no longer works on humans. Moreover, within Darwinian medicine, there is no ideological use of Darwinism, at least in relation to eugenic propositions. Finally, the topic of evolution of infectious disease, so important in medical Darwinism, remains central to Darwinian medicine, but without any implication of a Lamarckian evolutionary process in the evolution of bacteria.

Whereas the typological approach of medical Darwinism saw pathological traits as characters that escaped elimination by natural selection, the population approach of Darwinian medicine see disease as arising from vulnerabilities forced by compromises that are built and sometimes maintained by natural selection itself. This allows for an entirely new research program that can be implemented with quantitative and experimental methods. Nesse has written at length about how to create and test an evolutionary hypothesis (Nesse 2007), and the other major texts on Darwinian or evolutionary medicine present many experimental results relevant to medicine.

Finally, the authors of medical Darwinism, not being related to each other in a systematic framework, did not propose that medical Darwinism could be a new discipline. In fact, the term "medical Darwinism" did not exist at the time that they worked and wrote; it is simply an *a posteriori* historical construction. In contrast, contemporary Darwinian medicine is thought of by some authors as a basic science capable of unifying the medical sciences (Nesse et al. 2006; Nesse 2007; Nesse and Stearns 2008). Given that "Evolution is the vibrant foundation for all biology" (Nesse et al. 2006:1071), and given that medicine is founded on biology, evolution should be the "vibrant foundation" for all medicine too. This idea should have been evident for a long time, but it is still not widely accepted. Evolutionary biology should offer to biologists and doctors a basic perception of the nature of organisms. Because or-

ganisms are evolutionary products, they are a “bundle of careful compromises” (Nesse and Williams 1994:4). This idea is profoundly different from that of “body as machine,” so common in medicine, for the concept of machine implies a design or an engineer. Medicine probably still resists the full introduction and application of evolutionary thought exactly because it remains attached to the old idea of organism-machine, which has proved its practical and heuristic value for several centuries (it has permitted the emancipation of medicine from philosophy and religion since the Renaissance). Another reason for this resistance lies in the fact that evolutionary biology presents a sort of universal theory of disease, at least in the simple equation “vulnerability to disease = evolutionary product.” Doctors are still skeptical of every universal theory of disease, for the historical precedents are not encouraging. From the humoral theory to homeopathy, universal theories have proposed a common cause or scheme for almost all pathologies and a consequent miraculous panacea that has not been science, but fantasy. Darwinian medicine does not propose anything similar; on the contrary, evolutionary biology and Darwinian medicine are intimately founded in a multicausal approach to phenomena. Therefore, no universal therapy can exist.

I conclude this article with the following quotation, which I believe provides an ideal description of how to best carry out the potentialities of this new discipline—Darwinian medicine—that differs radically, as I hope to have shown, from the earlier attempts at “medical Darwinism.”

What actions would bring the full power of evolutionary biology to bear on human disease? We suggest three. First, include questions about evolution in medical licensing examinations; this will motivate curriculum committees to incorporate relevant basic science education. Second, ensure evolutionary expertise in agencies that fund biomedical research. Third, incorporate evolution into every relevant high school, undergraduate, and graduate course. These three changes will help clinicians and biomedical researchers understand that both the human body and its pathogens are not perfectly designed

machines but evolving biological systems shaped by selection under the constraints of tradeoffs that produce specific compromises and vulnerabilities. Powerful insights from evolutionary biology generate new questions whose answers will help improve human health. (Nesse et al. 2006:1071)

GLOSSARY

HUMORALISM.

A medical doctrine that arose in Greece around 400 BCE and that almost dominated medical thinking until the 18th century. This theory held that the human body was filled with four basic humors—black bile, yellow bile, phlegm, and blood—that are in balance when a person is in perfect health. The preponderance of one of these humors gives rise to a typical “temperament.” When blood dominates, we have a sanguine temperament; when phlegm is preponderant, we have a phlegmatic temperament; when yellow bile dominates, we have a choleric temperament; and, finally, when black bile predominates, we have a melancholic temperament. The theory of humors gradually lost influence until it was abandoned around the end of the 18th century, but the idea remained that bodily fluids, rather than solid parts of the body, are fundamental in the determination of diseases. For instance, in the first decades of the 20th century, the American physiologist Walter Cannon (1871–1945) proposed the concept of homeostasis, according to which the health of the body depends on the equilibrium of its fluid components, in particular blood and lymph. In contemporary medicine, the debate is rather around the preponderance of structural or functional derangements in disease, as there are some diseases that seem to result only from a functional problem referable to the excessive or defective expression of a gene, for instance, but also without any detectable structural change at the genetic level.

DIATHESIS.

An individual general tendency to a family of diseases due to the disorder—hereditary or acquired—of an organic system. The concept of diathesis is a very old one, but only in the 19th century did

it grow in popularity, and only at the end of the century do we find an established system of diatheses. At first, we find a myriad of different diatheses, differently defined by each doctor. For example, there is tuberculous diathesis—the tendency to develop tuberculous and/or malignant growth—due to a disorder of the so-called “system of absorption and excretion,” or there is nervous diathesis—the tendency to develop nervous diseases—due to a disorder of the nervous system, or cancerous diathesis, rheumatic diathesis, gouty diathesis, calculous, and so forth. Only at the end of the 19th century do we find a system of universal diatheses that belongs potentially to all humans. Each universal diathesis had an evolutionary nature and origin because it depended on the evolution of a particular system or organ. This view was founded on the theory of heredity typical of classical Darwinism (1860–1900). In addition to heredity of Mendelian type (*ante litteram* of course), this theory implicated the inheritance of acquired characters and so-called blending inheritance, or the possibility of forming intermediate characters by the fusion of paternal and maternal types viewed as fluids.

CONSTITUTION.

In medicine, constitution means the state of all organs of the human body considered in

their special arrangement, order, or activity (Dunglison 1848:213). Individual constitution is the sum of the somatic, functional, and psychological characteristics of each individual.

SOLIDISM.

The doctrine that attributes all diseases to morbid changes in the solid parts of the body. It rose to prominence as humoralism declined, around the end of the 18th century, and stood in contrast to that doctrine, which conceptualized all diseases as a disproportion of the bodily fluids or humors. In medicine, we can still find both the idea that diseases are due to a morbid change of a solid part of the body as well as the idea that diseases are due to a morbid change of a function without corresponding structural changes. These two visions are now complementary rather than mutually exclusive.

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