Ashdin Publishing
Journal of Evolutionary Medicine
Vol. 1 (2012), Article ID 235572, 12 pages
doi:10.4303/jem/235572

Review Article

HISTORY

Emergence of Evolutionary Medicine: Publication Trends from 1991–2010

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Received 9 April 2012; Accepted 24 August 2012

Abstract *Background.* Evolutionary medicine, the intersection of evolutionary biology and medical sciences, has grown in the last two decades. However, this new scientific discipline continues to have a limited impact in clinical medicine and medical education. As this field undergoes its own evolution, it has become necessary to better define this area of scientific inquiry by characterizing trends in publication, terminology, and the research focus of its practitioners. *Methods.* In order to identify publication trends in evolutionary medicine, the author performed a bibliometric analysis of citations related to evolution and medicine using PubMed, the ISI Web of Knowledge, Google Scholar, and the Google database of digitized books. *Results.* Usage patterns suggest that "evolutionary medicine" is supplanting its predecessor synonym "Darwinian medicine" in the scientific literature. In addition, the explosion in genomics and proteomics has resulted in a recent increase in medical research using phylogenetic techniques. Publications identified by searches for natural selection and adaptation are fewer in number and show linear growth in the literature. Keyword searches show that the terms "Darwinian medicine" and "evolutionary medicine" appeared more frequently than for the related terms "evolutionary psychiatry," "evolutionary epidemiology" or "evolutionary immunology." *Conclusions.* These results support the view that evolutionary medicine is a well-grounded concept that has emerged as a distinct area of scientific inquiry.

Keywords evolutionary medicine; Darwinian medicine; biological evolution; adaptation; natural selection; phylogeny; genetic drift; antibiotic resistance

1 Introduction

During the last two decades, many important insights in medicine have resulted from the application of evolutionary biology to the medical sciences, an endeavor that has been described as "evolutionary medicine" or "Darwinian medicine." Evolutionary (Darwinian) medicine uses the concepts of natural selection, adaptation, phylogenetics, and evolutionary constraints to understand health and disease. This approach has been used to understand aging [23, 55], redefine the concept of disease [21,39], explain why some features of the modern environment have adverse consequences on health [47], track the emergence of new diseases [58], understand genetic polymorphisms in human illnesses [16], and develop models to understand and manage bacterial resistance to antibiotics [6,44].

Despite these apparent successes, evolutionary medicine can be surprisingly difficult to characterize. Here, citation analysis is used to answer the question, "what is evolutionary medicine?" Although the usefulness of evolutionary biology in medicine has been described in many other publications [2,51], this review is focused on the characterization of evolutionary medicine as a concept and as the subject of scientific inquiry.

The principle of evolution by common descent, the idea that all living organisms share a common ancestor, has provided a unifying explanation for various similarities and differences between biological forms since the time of Darwin [9], providing an organizing principle to a wide variety of biological disciplines, such as systematics and cladistics [31]. Increasingly, evolution has also been applied to a variety of topics that relate to medicine, from epidemiology and medical anthropology [46] to infectious disease [8,15]. Just as biologists argue whether two related groups are sufficiently similar to be lumped into a single taxon, or split into two, observers of evolutionary medicine may argue about its place in the scientific universe. It has been unclear whether evolutionary medicine is its own discipline or rather a subdomain of evolutionary biology [30]. Others have questioned whether evolutionary medicine is a cohesive research tradition or consists instead of loosely aligned scientists pursuing different research agendas [33].

Unlike many areas of biology, medical research has not yet been shaped by a foundation of evolutionary biology. In fact, adding the descriptor "evolutionary" to medicine suggests a need to distinguish this concept from some non-evolutionary alternative. Along these lines, Williams and Nesse [57] proposed that evolutionary medicine allows a substantively different viewpoint than can be found elsewhere in medicine. They argued that evolutionary medicine yields novel predictions about medical phenomena compared with the non-evolutionary, mechanistic approach to physiology and health. In addition, Nesse and others have advocated for increased acceptance of evolution as a foundational science for medicine [18, 57]. Meanwhile, some biomedical disciplines that are not generally considered "evolutionary medicine" already take an approach that relies on the evolutionary principle of common descent. For instance, much research in genomics, proteomics and bioinformatics applies phylogenetic methodologies to questions of medical importance [50].

In this paper, I examine subject identifiers relevant to evolution in the National Library of Science (NLM) to determine the status of evolutionary biology in the medical literature. Medical Subject Headings (MeSH), a controlled terminology used to index publications in Medline, were first published in 1963, with 5,700 terms. Today, there are more than 25,000 terms. MeSH terms are updated annually by NLM. Because MeSH terms are used for the classification and retrieval of publications in the health and biomedical literature, they can be used to track the emergence of new areas of science [10, 32]. Thus, MeSH terms provide a window into the use of evolution in the medical sciences.

I also review the social features that have been described as necessary benchmarks in the development of a new scientific discipline. These milestones include the emergence of informal networks of physicians and scientists as well as institutions that permit collaborative work in evolutionary medicine. Finally, I examine whether sufficient scientific gatherings, conferences, and training activities provide the substrate for evolutionary medicine to develop as a distinct scientific field.

2 Methods

I performed a comprehensive literature search using the databases PubMed, The ISI Web of Science, and Google Scholar, to assess trends in the use of evolutionary concepts in the medical and general scientific literature. In each search, the number of articles was recorded for every year between 1991 and 2010. This time frame includes 1991, the year of publication of evolutionary biologist George C. Williams and psychiatrist Randolph Nesse's influential article "Why we get sick, the dawn of Darwinian medicine" [57]. This time frame also includes 2009, the 200th anniversary of Charles Darwin's birth.

Because PubMed is widely used by physicians and biomedical researchers, citations found in this database are likely to be visible to the medical community. PubMed includes scientific citations from Medline, journals in the life sciences, and electronic books indexed by the National Library of Medicine. The ISI Web of Science database surveys the general scientific literature and includes disciplines not included in PubMed, such as veterinary science and ecology. A limitation of this database, however, is that only ISI journals are listed. Another resource for bibliometric analysis, Google scholar, is increasingly used in the scientific community. A wide variety of source documents, including books, journal titles, and book reviews, are identified by Google scholar searches, though the source coverage is not well defined.

I performed literature searches using the keywords "Darwinian medicine" and "evolutionary medicine" to identify MeSH terms mapped to publications thus identified. Throughout this manuscript, MeSH terms (e.g., **Biological Evolution**) are designated in capitals, as they appear in the NLM MeSH browser, and in bold type. These MeSH terms were used to generate additional searches of PubMed, to assess how evolution is indexed in the medical literature in the two-decade time period from 1991 to 2010. PubMed searches performed in the paper were limited to dates from 1991 to 2010. All PubMed searches were limited to humans, which tended to increase the relevance of citations to humans and diseases of humans. In each search, duplicate results were removed if they were identified. Publication dates, if variable, were restricted to the print publication date. I searched these databases during December 2011 to April 2012.

For PubMed searches of many MeSH terms, citations were screened for relevance to evolutionary medicine, using the most recent 100 publications in each sample. Publications in the medical and scientific literature were deemed relevant to evolutionary medicine if they met these three criteria: (1) they included evolutionary concepts (e.g., Darwinian evolution, molecular evolution, phylogeny, selection, adaptation, genetic drift, or genetic fitness); (2) they were concerned with humans (human physiology, genetics, immunity, ancestry) or other organisms that play a role in human health (e.g., HIV, influenza, mosquitoes, commensal microbes); (3) they were related to human health or disease (e.g., infection, trauma, neoplasia, and longevity) (Figure 1).

To determine trends in the non-technical literature, I used a database of millions of digitized books, made accessible with the Google books N-gram viewer. The Google N-gram viewer allows searches of the database of digitized books using a single keyword (1-gram), a two-word phrase (2-gram) or any number of words in sequence (N-gram, where N is the number of words). Results are displayed as a percentage of the specific N-gram's appearance in relation

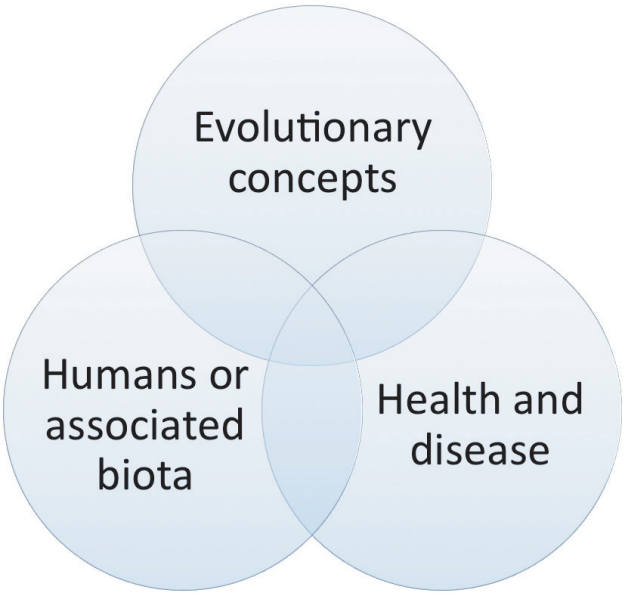

Figure 1: Criteria used to determine relevance to evolutionary medicine for citations in PubMed. Citations were judged to be relevant to evolutionary medicine if they (1) included an evolutionary topic (see methods for additional details), (2) included humans or organisms associated with human illness (such as bacteria, viruses, arthropods that are disease agents or vectors, or microbes that provide protection from illness), and (3) discussed human health or disease. By this definition, evolutionary medicine is illustrated by the area of overlap that these three domains have in common.

to all other N-grams in the database. This approach has been used to quantitatively investigate trends in the use of language [34]. We used the Google books digitized database and the N-gram viewer to compare evolutionary terminology in the health sciences, such as evolutionary medicine, Darwinian medicine, and evolutionary epidemiology.

3 Results

3.1 Growth in publications relating to evolution in health and disease

Publication of articles on evolutionary topics has shown a steady growth during the last two decades (Figure 2). A search of PubMed using the MeSH terms **Biological Evolution** and **Medicine** identified only 5 publications in 1991. The number of publications meeting those search criteria increased to 209 results in 2010 with a maximum of 277 publications in 2009. The peak in publications in 2009 coincides with the bicentennial of Darwin's birth and the 150th anniversary of the publication of *On the Origin of Species* [9]. The increase in PubMed indexed publications with the MeSH terms **Biological Evolution** and **Medicine** corresponds to an average annual rate of increase of 26.5%.

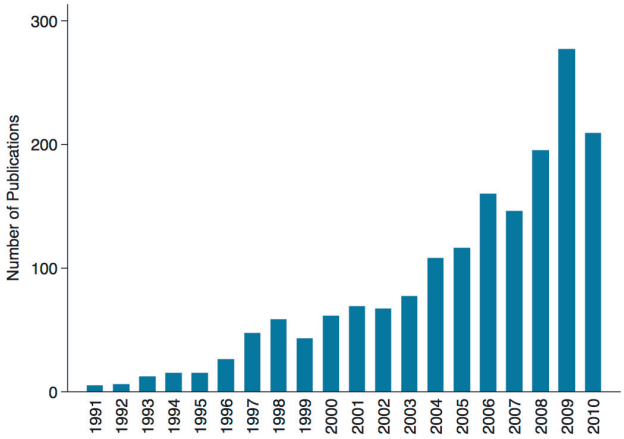

Figure 2: PubMed citations with the combined MeSH terms **Biological Evolution** and **Medicine** published between 1991 and 2010.

To ensure that this increase is not a result of growth in the number of indexed publications overall, I performed a control search using the MeSH term **Humans**. PubMed citations with this MeSH term increased from 260,956 in 1991 to 514,321 in 2010, representing an average annual increase for this search of 3.6%. This figure is similar to the 4% average annual increase in overall PubMed citations that has been reported elsewhere [10]. As a result, the increase in evolutionary topics in PubMed outpaced the general growth in scientific publication during the time frame we examined.

3.2 "Evolutionary medicine" is preferred over "Darwinian medicine"

A PubMed search for the keyword "Darwinian medicine" yielded only 39 publications between 1991 and 2010. A similar search with the keywords "evolutionary medicine" produced 97 results. This search also identified academic institutions having titles that included the words "evolutionary medicine." Some of these institutions are pursuing research relevant to evolutionary biology in health and disease (Table 1). Yet, 17 publications from these centers did not relate to evolution or did not relate to health and disease. After excluding these false positives, only 94 publications identified by "Darwinian medicine" or "evolutionary medicine" had been assigned MeSH terms. Eighty four publications included the Mesh term **Humans** (89%). The next most common MeSH term was **Biological Evolution**, in 62 (66%). An additional 11 publications were identified with **Evolution, Molecular** (12%) (Table 2). Notably, the widely cited [57] publication entitled "The dawn of Darwinian medicine" was not assigned the MeSH term **Biological Evolution**; instead, this publication was mapped to Adaptation, **Physiological/genetics** and **Selection, Genetic** (Figure 3). Descriptions of each of these MeSH terms are found in Table 3.

Table 1: Literature searches using PubMed identified several academic centers that study evolutionary medicine.

Institutions with names that include evolutionary medicine
Centre for Evolutionary Medicine, Institute of Anatomy, University of Zurich, Switzerland http://evolutionaeremedizin.ch/ Recent representative citation: Harris lines revisited: Prevalence, comorbidities, and possible etiologies [43].
Center for Evolutionary Medicine and Informatics, The Biodesign Institute, Arizona State University, Tempe, AZ, USA http://www.biodesign.asu.edu/research/research-centers/evolutionary-medicine-and-informatics Recent representative citation: Timing the origin of human malarias: The lemur puzzle [42].
Evolutionary Medicine Unit, University of the Witwatersrand and National Health Laboratory Service, Johannesburg, South Africa http://www.wits.ac.za/pathology/emu/9334/evolutionarymedicineunit.html Recent representative citation: Genomics in the light of evolutionary transitions [11].
Other academic centers studying evolution in medicine
Liggins Institute, Centre for Human Evolution, Adaptation, and Disease, University of Auckland, New Zealand http://evomedicine.org/ Recent representative citation: Plasticity and robustness in development and evolution [4].
Center for Evolutionary and Theoretical Immunology, University of New Mexico, Albuquerque, NM, USA http://ceti.unm.edu/ Recent representative citation: The primary role of fibrinogen-related proteins in invertebrates is defense, not coagulation [20].
Center for Evolution and Cancer, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA http://cancer.ucsf.edu/evolution Recent representative citation: Overlooking evolution: A systematic analysis of cancer relapse and therapeutic resistance research [1].

Table 2: The frequency of selected MeSH headings of 94 citations identified with keywords "Darwinian medicine" or "evolutionary medicine" in PubMed. MeSH headings designated as major topics are also shown.

MeSH term	Number (%)	Major
Humans	84 (89%)	0
Biological Evolution	62 (66%)	13
Selection, Genetic	23 (24%)	10
Adaptation, Physiological	13 (14%)	6
Evolution, Molecular	11 (12%)	6
Medicine	11 (12%)	11
Adaptation, Biological	7 (7%)	1
Phylogeny	3 (3%)	1

The dawn of Darwinian medicine.

Williams GC, Nesse RM

Quarterly Review of Biology. 1991

While evolution by natural selection has long been a foundation for biomedical science, it has recently gained new power to explain many aspects of disease. This progress results largely from the disciplined application of what has been called the adaptationist program. We show that this increasingly significant research paradigm can predict otherwise unsuspected facets of human biology, and that it provides new insights into the causes of medical disorders...

MeSH Terms

Adaptation, Physiological/genetics
Animals
Environment
Genetics, Medical
Humans
Models, Genetic
Selection, Genetic*

Figure 3: Abstract and MeSH headings assigned by the National Library of Medicine to the landmark paper by Williams and Nesse [57] that introduced the term "Darwinian medicine," more commonly referred to now as "evolutionary medicine." *__Selection, Genetic__ was designated by NLM to be a major topic of the article.

Keyword searches with the commonly used database, ISI Web of Knowledge, using the keywords "evolutionary medicine" or "Darwinian medicine" also suggest that these terms are not in widespread use. These terms appeared first in 1991 [57] with maximum frequency of 41 publications in 2009 (Figure 4) in the ISI Web of Knowledge database. Over the last 10 years, "Darwinian medicine" has been largely supplanted with the synonym "evolutionary medicine," which appeared in 39 of 41 publications in 2009. This shift in terminology, while more inclusive, makes it harder to identify relevant articles, because the word "evolution" is commonly used in medicine to denote generic change without implying biological evolution (e.g., see [49]).

A Google scholar search with the keywords "evolutionary medicine" returned 2211 results between 1991 and 2010 (excluding patents and including citations). A similar search using "Darwinian medicine" identified fewer citations (1370). The pattern of growth in citations using "evolutionary medicine" has been exponential over the last two decades (Figure 5). The number of results using Google scholar (400 citations in 2010) was higher than those returned by PubMed or ISI Web of Knowledge searches and included citations such as book chapters, book reviews, and other writings that are not included elsewhere.

Table 3: Concepts and definitions of selected Medical Subject Headings that relate to evolution, as provided by the National Library of Medicine. *In the MeSH tree structure, terms exist in a hierarchy (or hierarchies). Certain terms (e.g., **Evolution, Molecular**) are indexed under other terms (e.g., **Biological Evolution**). Thus a PubMed search for **Biological Evolution** may also return citations identified by **Evolution, Molecular**, depending on the specification of the search.

MeSH term	Concepts included	Definition (from MeSH Descriptor Data)	Indexed under*
Biological Evolution	Biological evolution	The process of cumulative change over successive generations through which organisms acquire their distinguishing morphological and physiological characteristics.	Genetic Processes
Evolution, Molecular	Directed molecular evolution Genetic evolution	The process of cumulative change at the level of DNA, RNA and proteins, over successive generations.	Biological Evolution
Selection, Genetic	Genetic selection Natural selection	Differential and non-random reproduction of different genotypes, operating to alter the gene frequencies within a population.	Genetic Processes
Adaptation, Physiological	Physiological adaptation	The non-genetic biological changes of an organism in response to challenges in its environment	Adaptation, Biological Physiological Processes
Adaptation, Biological	Biological adaptation	Changes in biological features that help an organism cope with its environment. These changes include physiological	Biological Processes
Phylogeny	Phylogenetics	The relationships of groups of organisms as reflected by their genetic makeup	Biological Evolution Genetic Phenomena
Genetic Drift	Genetic Drift Neutral Evolution	The fluctuation of the allele frequency from one generation to the next.	Biological Evolution Genetic Phenomena

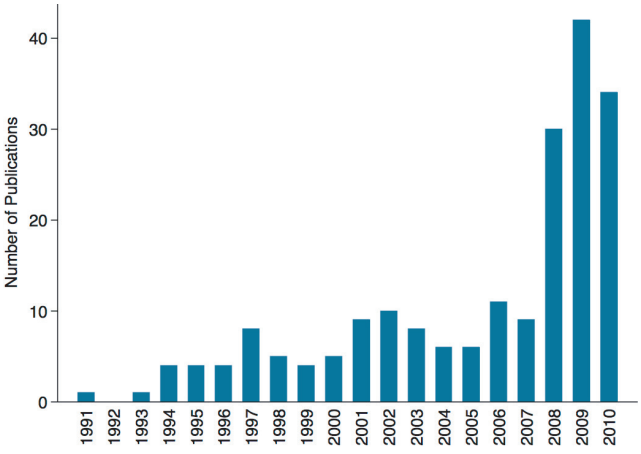

Figure 4: ISI Web of Knowledge citations with terms "Darwinian medicine" or "evolutionary medicine" published between 1991 and 2010.

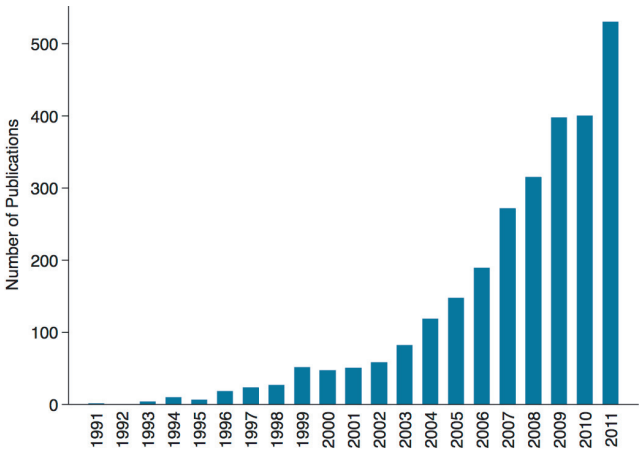

Figure 5: Google scholar citations with keywords "evolutionary medicine." Citations from 1991 to 2011 are included; the continued climb in 2011 suggests that the apparent decline in citations related to evolution in 2010 in Figures 2 and 4 may not reflect long-term trends.

3.3 Changes in terminology in digitized books

A digitized book database provided another measure of scientific and cultural trends in the use "Darwinian medicine" and "evolutionary medicine." Google books is a database of millions of digitized books comprising about 4% of the corpus of all published books. This database of digitized books suggests that these terms were first used in books around 1990 (Figure 6). During the last two decades, "Darwinian medicine" occurred more frequently than "evolutionary medicine" in digitized books, although recent usage suggests that the use of "evolutionary medicine" will overtake the alternative phrase (Figure 6). Additional keyword searches show that both of these terms ("Darwinian medicine" and "evolutionary medicine") have been used more frequently than the related phrases "evolutionary psychiatry, evolutionary epidemiology," and "evolutionary immunology" (Figure 6).

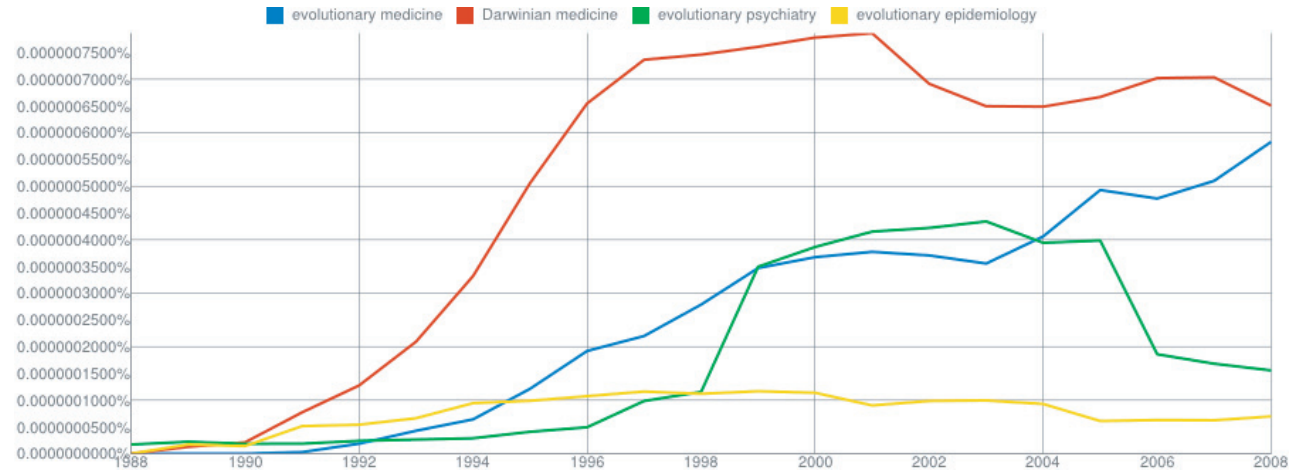

Figure 6: Google n-gram viewer results showing the percentage of these two-word phrases that appear in a database of digitized books. Here, evolutionary medicine is displayed with related phrases during 1988–2008. (2008 was the most recent year available.)

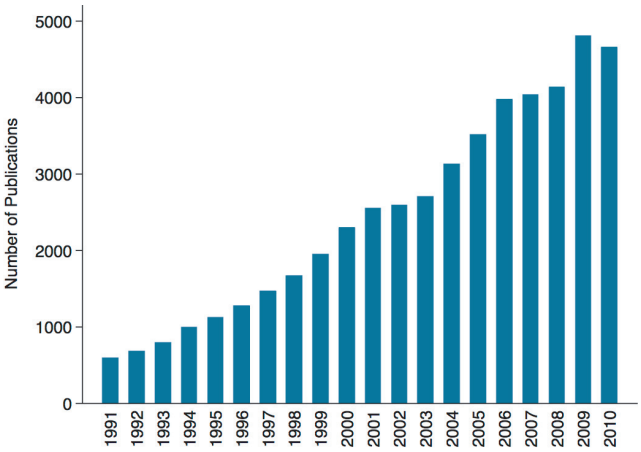

Figure 7: PubMed citations with the MeSH term **Biological Evolution** published between 1991 and 2010.

3.4 Biological Evolution

The MeSH terms identified in Table 2 were used to generate additional searches to determine how evolutionary concepts have been indexed in the National Library of Medicine. The NLM introduced the MeSH heading **Evolution** in 1966, antedating the Williams and Nesse [57] paper by several decades. The Mesh term in current use, **Biological Evolution**, was updated in 2011, to distinguish it from other forms of evolution (e.g., cultural). Overall, publications identified with **Biological Evolution** have experienced an average annual rate of growth of 11.6% since 1991 (Figure 7).

The growing number of publications indexed to **Biological Evolution** (Figure 7) shows that evolution is already a basic science for many researchers in biomedicine and related fields. These works require knowledge of basic evolutionary concepts, particularly an understanding of homology and evolution by common descent. Of course, not all of citations identified with **Biological Evolution** are directly relevant to human health. Some works describe features of human biology that are unrelated to health or characterize microbes or other species that are not important as disease-agents. Also, some of these papers are less evolutionary (a mere mention) and some more so (a major theme). While it is possible to restrict results to major MeSH headings, the results shown in Table 2 indicate that such an approach using **Biological Evolution** will miss many self-identified works in evolutionary medicine.

3.5 Molecular Evolution and Phylogeny

A search using **Evolution, Molecular** yielded 14,017 publications. Molecular Evolution is defined in MeSH as "The process of cumulative change at the level of DNA, RNA, and proteins, over successive generations" (Table 3). Publications describing "evolutionarily conserved" homologous protein or gene sequences, for instance, are also often mapped to this MeSH term. While it might seem that these approaches would fall under the rubric of evolutionary medicine, a combined search of **Evolution, Molecular** AND "evolutionary medicine" in PubMed yielded only 4 results between 1991 and 2010.

Phylogeny is mapped to only 3 of publications (3%) with the keywords evolutionary medicine or Darwinian medicine in PubMed (Table 2). By contrast, **Phylogeny** was indexed to 23,762 publications between 1991 and 2010 using our search methodology. Thus, **Phylogeny** is one of the more frequently indexed evolutionary terms in PubMed. **Phylogeny** is found under **Biological Evolution** in the

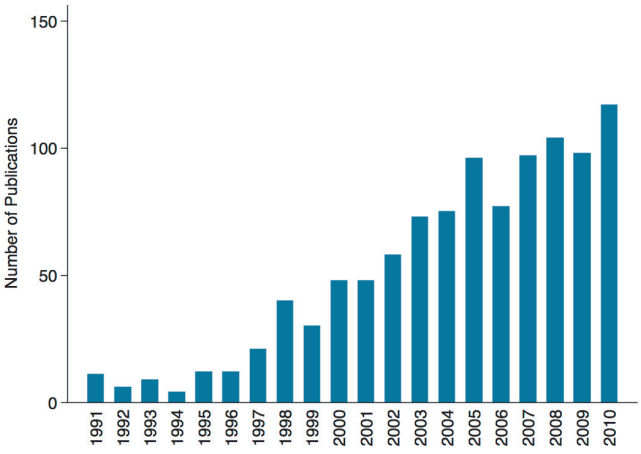

Figure 8: PubMed citations with the MeSH headings **Biological Evolution** and **Adaptation, Biological**, published between 1991 and 2010.

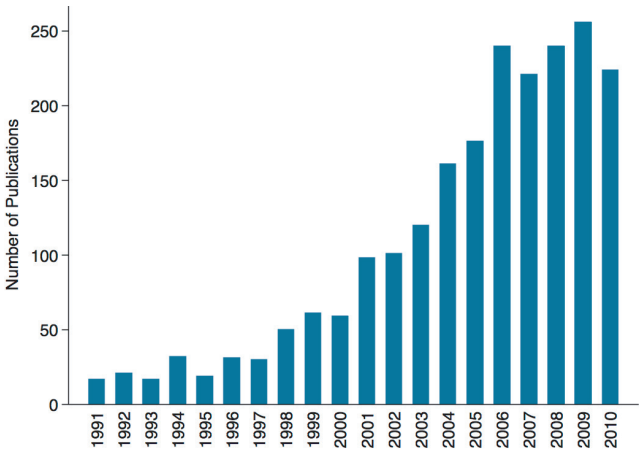

Figure 9: PubMed citations with the MeSH headings **Biological Evolution** and **Selection, Genetic**, published between 1991 and 2010.

MeSH hierarchy as is **Evolution, Molecular** (Table 3). Of the 100 most recent citations in 2010 using **Phylogeny** and the search filter limited to humans, 26 (26%) met the criteria for relevance to evolutionary medicine (Figure 1). Consideration of phylogenetic studies in biomedicine indicates that research at the interface of evolution and medicine is much more pervasive than is suggested by searches based on terms such as "evolutionary medicine."

3.6 Adaptation and Natural Selection

The concept of adaptation by natural selection is represented by one of several MeSH terms. Some are indexed with the term **Adaptation, Biological** (e.g., [37]), but most are mapped to **Adaptation, Physiological** (e.g., [13]) (Tables 2 and 3), which is subordinate to **Adaptation, Biological** in the MeSH tree structure (Table 3). Although neither of these terms matches perfectly with the concept of adaptation in the Darwinian sense of increasing survival or fitness, these MeSH terms were often assigned to publications identified by keywords "evolutionary medicine" or "Darwinian medicine" (e.g., Table 2). Publications indexed to **Adaptation, Physiological/genetics** were relevant to evolutionary medicine in 29 (30%) of 87 citations published in 2010 with the search filter limited to humans. Combining the **Adaptation, Biological** AND **Biological Evolution** results in 1037 publications between 1991 and 2010 (Figure 8).

Meanwhile, the concepts of genetic fitness or natural selection map to the term **Selection, Genetic**. **Selection, Genetic** is found under **Biological Evolution** in the MeSH tree structure (unlike **Adaptation, Biological**; see Table 3). A search using **Selection, Genetic** yielded 4271 publications (Figure 9), with the search filter limited to humans. Of the 440 that were published in 2010, 172 (39%) were relevant to evolutionary medicine by the criteria in Figure 1. Of the evolution-related MeSH terms, **Adaptation, Physiological/genetics** and **Selection, Genetic** identify citations that are relevant to evolutionary medicine more often than the terms **Evolution, Molecular** or **Phylogeny**. However, publications with adaptation as a main focus were relatively fewer in number and the rate of publication growth has tapered over the last decade (Figure 8).

Genetic change that is neutral to natural selection is termed "neutral evolution" and can occur by genetic drift. These concepts are included in the MeSH term **Genetic drift** (Table 3), which identified only 303 publications between 1991 and 2010. Of the 36 publications using Genetic Drift, published in 2010 and limited to humans, 8 (22%) met the criteria for evolutionary medicine.

3.7 Search strategies for evolutionary medicine

Searches for the keywords "evolutionary medicine" yielded more than 10 times the number of citations than similar searches using "Darwinian medicine" (without quotation marks) in both the PubMed and ISI Web of Knowledge. Many of these search results, however, do not relate to human diseases or do not relate to biological evolution. Use of the exact phrase, by including quotation marks, decreases the yield of searches but produces more relevant results (higher specificity) (Figure 4). One effective strategy is to use the MeSH heading **Biological Evolution**, or any of the MeSH terms in Table 3, in combination with another search term (e.g., "malaria" or "cancer"). Use of the search engine Google Scholar with the keywords "evolutionary medicine" also yields a high number of relevant citations ($>$ 80%) (Figure 4). One caveat to this approach is that not all citations produced by Google scholar are, in fact, scholarly.

Table 4: A selection of journals that publish research on evolutionary medicine. The top 5 journals for three representative searches are shown. See text for additional details. Search results were screened for relevance for evolutionary medicine by the author. Impact factors are recorded for the year 2010. Eigenfactor is an alternative metric for assessing impact; these were recorded from eigenfactor.org during March–April 2012.

Journal	PubMed search	Impact factor	Eigenfactor
AIDS Research and Human Retroviruses	**Phylogeny**	2.082	0.0119
American Journal of Human Biology	"Evolutionary medicine" or "Darwinian medicine"	2.021	0.0062
BMC Evolutionary Biology	**Selection, Genetic**	3.70	0.0396
Emerging Infectious Diseases	**Phylogeny**	6.859	0.0737
Infection, Genetics and Evolution	**Selection, Genetic**	3.086	0.0081
International Journal of Antimicrobial Agents	**Selection, Genetic**	3.79	0.0197
Journal of Clinical Microbiology	**Phylogeny**	4.22	0.0980
Journal of Medical Virology	**Phylogeny**	2.895	0.0214
Journal of the Royal Society of Medicine	"Evolutionary medicine" or "Darwinian medicine"	1.366	0.00419
Journal of Virology	**Selection, Genetic**	5.189	0.2123
Medical Hypotheses	"Evolutionary medicine" or "Darwinian medicine"	1.389	0.0127
PLoS One	"Evolutionary medicine" or "Darwinian medicine" **Phylogeny**	4.411	0.3196
Proceedings of the National Academy of Sciences USA	"Evolutionary medicine" or "Darwinian medicine" **Selection, Genetic**	9.771	1.6592
The Quarterly Review of Biology	"Evolutionary medicine" or "Darwinian medicine"	5.818	0.0339
Science	"Evolutionary medicine" or "Darwinian medicine" **Selection, Genetic**	31.36	1.4555

3.8 Journals that publish evolutionary research in biomedicine

Several journal titles were over-represented in the sample of search results. PubMed citations with keywords "evolutionary medicine" or "Darwinian medicine" appeared most often in Medical Hypotheses, the American Journal of Human Biology, The Quarterly Review of Biology, the Journal of the Royal Society of Medicine, and Science (Table 4).

Among the 100 most recent publications with the MeSH term **Selection, Genetic**, screened for relevance to evolutionary medicine, the top 5 most frequent journals were Proceedings of the National Academy of Sciences USA, Science, Journal of Virology, Infection, Genetics and Evolution, International Journal of Antimicrobial Agents and BMC Evolutionary Biology.

Publications with the MeSH term **Phylogeny** were found most often in The Journal of Clinical Microbiology, Public Library of Science (PLoS) One, AIDS Research and Human Retroviruses, Journal of Medical Virology, and Emerging Infectious Diseases. Each of these searches in this section used the PubMed database so results were limited to journals indexed in that database. It is notable that some journals that publish works in evolutionary medicine, including the Journal of Evolutionary Medicine, are not yet included in PubMed. As a result, PubMed searches may underestimate the total number of publications in this research area.

4 Discussion

Evolutionary medicine is a relatively new and developing area of scientific inquiry that is defined as the application of Darwinian evolutionary principles to health and disease. Although evolutionary concepts appeared in the medical literature dating to the turn of the last century [59], the application of modern evolutionary thought has not been influential in the medical sciences until recently. In fact, the terms "Darwinian medicine" and "evolutionary medicine" entered the lexicon around 1990 [57]. Thus, for most of the 20th century, the health sciences and evolutionary biology progressed along different paths, with neither discipline having much impact on the other. Recently, this has begun to change (Figures 1, 3, and 4). The last 20 years have seen an increased exchange of information between the two fields of study, a trend that has accelerated in recent years [51]. In particular, over the last two decades, advances in genomics and bioinformatics have made the use of phylogenetic techniques in medicine commonplace; these techniques have helped define the taxonomy, epidemiology, and pathogenesis of many important human pathogens [29, 58]. Indeed a new term, "phylomedicine," has been coined to describe the evolutionary research approach used to explore genetic diversity involved in disease [25]. Apart from phylogenetics and phylomedicine, evolutionary hypotheses involving adaptation and natural selection of humans make a consistent appearance in the biomedical literature (Figures 7 and 8).

The application of evolutionary biology to clinical medicine has been hindered by the absence of education in evolution in medical school. Few medical schools include evolutionary biology in the medical school curriculum. Because teaching of evolution in medical schools is inconsistent (or absent), it is unsurprising that many physicians are unfamiliar with evolutionary applications in the health sciences [41]. Other barriers to more widespread use of evolution in medicine include the lack of a MeSH search heading for evolutionary medicine and ambiguity in the literature regarding the preferred term: "evolutionary medicine" versus "Darwinian medicine" [33].

In some respects, this review of the literature suggests that concern about the acceptance of evolutionary medicine is misplaced. Despite the limitations of the search methodology, the overall trend in publication suggests an exponential pattern during the last two decades (Figures 2, 4, and 5). This increase has outpaced the growth of publication in biomedical sciences which have roughly doubled in the decade that ended in 2010 compared with the previous 10-year period. The frequent appearance of evolution in citations indexed by the NLM, including many publications relevant to evolutionary medicine in the most widely cited journals, indicates an increasing acceptance of evolution in medicine and related sciences. One caveat in noting this positive trend is that the anniversary of Darwin's birth in 2009 and the publication of *On the Origin of Species* [9] may have sparked a temporary uptick in interest in evolutionary topics.

Darwin's *On the Origin of Species* was a book length argument for two revolutionary ideas. First, Darwin presented a detailed argument for incremental intergenerational change, culminating in the emergence of new species. This explanation, emphasizing gradual change and common descent, is at the core of today's phylogenetic approaches. The second idea was an explanation of a mechanism of evolution: adaptation by natural selection, an idea that was also independently discovered by Alfred Wallace [54]. A dichotomy in focus (between phylogeny and adaptation by natural selection) in the evolutionary medical literature reflects the two main concepts described in *On The Origin of Species* [9]. While natural selection is less often discussed in the medical compared to the biological literature, influential works in medicine have used this approach. Two notable early examples include the well-validated hypothesis that a heterozygote advantage of sickle cell allele carriers improves survival from *falciparum* malaria [3] and James Neel's proposal that energy-conserving "thrifty" genes explain the epidemiology of type II diabetes [38]. One possible explanation for the relative unpopularity of hypotheses involving natural selection in medicine may be the enduring effect of Gould and Lewontin's critique of the adaptationist approach [19]. Gould argued that adaptation by natural selection is not the dominant force in evolution and asserted that complex features of biological systems evolve as byproducts, not as the result of selection for a particular function. More than 30 years later, adaptation in evolutionary medicine has been criticized as misguided and possibly dangerous [53]. Ample research in evolutionary medicine challenges these viewpoints. Examples include selection for lactase persistence in human populations with dairying traditions [12,52], evidence of selection for adaptation to high altitude among Andeans and Tibetans [5, 48], and the role of selection in causing and controlling antibiotic resistance [22,27,35]. Adaptation and natural selection have also been applied to medical phenomena such as fever [24,57], the determinants of pathogen virulence [14, 15], and the evolution of drug resistance in neoplasms [1, 26]. These and many other studies demonstrate the heuristic value of applying the concepts of adaptation and natural selection to biomedical problems and they show that hypotheses using adaptation are testable.

It should not come as a surprise that MeSH terms for the concepts of adaptation and selection (Table 3) identify citations that tend to be more relevant to evolutionary medicine than other evolutionary MeSH terms. One of evolutionary medicine's first proponents, the preeminent evolutionary theorist George C. Williams, wrote the highly influential book *Adaptation and Natural Selection* [56]. Fittingly, **Adaptation** and **Selection, Genetic** were the evolutionary MeSH terms assigned to Williams and Nesse's (1991) article entitled "the dawn of Darwinian medicine." According to Nesse [40], George C. Williams advocated for the eponymous "Darwinian" label because of its connection to natural selection. Given this history, "Darwinian medicine" might be seen as the subset of evolutionary medicine that deals primarily with adaptation and natural selection. This point of view has been articulated by Lewis [28], who argued that "evolutionary medicine" allows for a more comprehensive array of evolutionary explanations in biomedicine. Recently, Nesse [40] also endorsed inclusive terminology that broadly covers evolutionary work in health and disease. Co-incident with the shift away from "Darwinian medicine," many recent PubMed-indexed publications are mapped to evolutionary MeSH terms other than **Adaptation** and **Selection**.

Méthot [33] has pointed out that a disadvantage of a broad definition of evolutionary medicine is the lack of internal cohesion of this research area. Although the MeSH term **Phylogeny** accounts for nearly half of the publications indexed under **Biological Evolution** in PubMed, few of these citations self-identify as "evolutionary medicine" (Table 2). However, the last decade has given rise to "evolutionary genomics" [50] and "phylomedicine" [25], which explicitly take an evolutionary approach to health and disease. The growth of phylogenetic techniques in medicine provides a strong additional rationale for teaching evolution

in medical schools. Recent events, such as the recent H1N1 influenza pandemic and the ongoing epidemic of HIV have reinforced the need to use phylogenetic techniques to uncover the origin and spread of emerging diseases and to monitor evolution of resistance and virulence of pathogens. The ability to understand evolutionary concepts, such as common descent and homology, is a prerequisite to perform and interpret these phylogenetic analyses [45].

4.1 Evolutionary medicine as a developing science

Sociologists and historians of science have proposed several metrics to determine how areas of science emerge and develop. Crane [7] and others have suggested that scientific disciplines undergo several stages. Among these is a stage of logistic growth. Evolutionary medicine has undergone exponential growth, illustrated in Figures 1 and 7. This increase is less impressive than in some other emerging disciplines. For example, the term nanotechnology appeared at about the same time as evolutionary medicine (e.g., [17]). Since then, research in nanotechnology has undergone explosive growth, with over 33,000 MeSH search results in PubMed. The MeSH term Nanotechnology was established in 2002. Exponential growth does not seem to be a prerequisite for the definition of a new research area or introduction of a new MeSH term, however. Some areas of research with little publication activity have their own MeSH terms (Figure 10). For example, Wilderness Medicine was introduced in 2009. Wilderness medicine is the study and practice of medicine in remote or austere environments. In contrast to evolutionary medicine, which has not, until recently, had its own journal or organized scientific society, the Wilderness Medical Society began publishing the journal Wilderness and Environmental Medicine in 1990. Notably, however, **Wilderness Medicine** is mapped to only 36 publications. The pattern of research activity and publication in evolutionary medicine far outpaces that of wilderness medicine. The trajectory of citation growth supports the introduction of a new MeSH term for evolutionary medicine.

A new MeSH term for evolutionary medicine could help circumvent some of the limitations of existing search strategies used by scholars interested in evolution in health and disease. The contrast in citation numbers between Figures 4–5 and Figure 7 show that many articles using evolutionary concepts in biomedicine do not include the keywords "evolutionary medicine" (or "Darwinian medicine"), and are missed by searches using those terms. Also, many citations with evolutionary MeSH terms are not relevant to evolutionary medicine. Only 20–40% of citations meet the 3 criteria proposed in this review for relevance to evolutionary medicine. The subset of relevant search results, though smaller than the overall number of publications with evolutionary MeSH terms, includes many hundreds of citations relevant to evolutionary medicine that

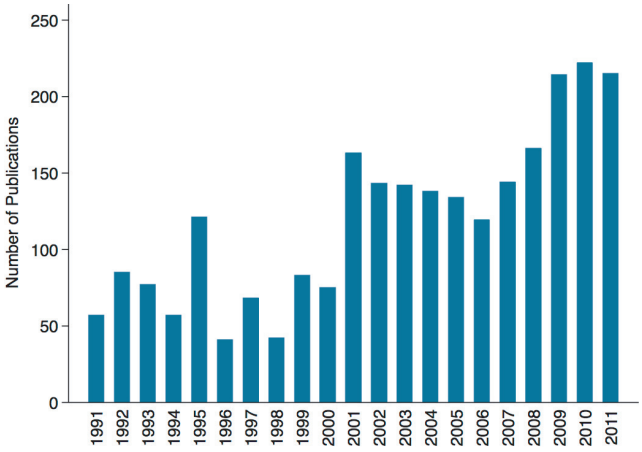

Figure 10: Google scholar citations with keywords "Wilderness Medicine" published between 1991 and 2011.

are published each year. An important limitation of these criteria (Figure 1), and their application to PubMed search results, is that they are subject to personal judgment. Others may disagree with these criteria and propose additional distinctions to identify evolutionary medicine from non-evolutionary medicine. One goal of this review is to stimulate discussion among participants in this emerging field regarding the scope and breadth of evolutionary medicine.

4.2 Scientific networks in evolutionary medicine

Social networks, formal and informal, have been described as a necessary feature for the establishment of a new area of science [36]. In tandem with the growth in the number of evolutionary medicine publications, increasing options have become available for networking and social interaction among researchers and clinicians interested in evolutionary medicine. Academic centers with a focus on themes in evolutionary medicine have appeared in recent years (Table 1). Although it has been suggested that informal networks of working researchers, the so-called "invisible college," are central to the emergence of a new scientific discipline (e.g., [7]), evolutionary medicine-themed academic centers offer a highly visible marker of this emerging field. The existence of these institutions satisfies a pre-condition for the greater acceptance of evolutionary medicine posed by Williams and Nesse [57]:

"The substantial benefits of evolutionary studies of disease will be realized only if they become central to medical curricula, an advance that may at first require the establishment of one or more research centers dedicated to the further development of Darwinian medicine."

In addition, opportunities for networking are posted at the website The Evolution and Medicine Review (http://evmedreview.com/). The same site maintains an

updated calendar of scientific meetings on the topic of evolutionary medicine, of which there were 13 in 2010 and 11 listed in 2011. A recent option for practicing physicians and other professionals, available as of 2011, is the opportunity to earn continuing medical education during a one-week summer course on evolution and health and medicine at the Mount Desert Island Biological Lab in Maine. In another first, Durham University in the UK recently initiated a graduate training program culminating in a Master's of Science degree in Evolutionary Medicine, starting in the 2011/2012 academic year. These options for teaching and learning evolutionary medicine suggest that (1) evolution is gaining acceptance as a basic science for medicine and (2) the social substrate for this new field is taking shape.

5 Summary and conclusions

(1) Evolutionary (Darwinian) Medicine shares themes with molecular biology, evolutionary biology, and clinical medicine. The emphasis on evolutionary concepts applied to health-related features of human and microbial biology render evolutionary medicine a recognizable and distinct area of science. Evolutionary medicine has experienced an exponential growth in the scientific literature since its formal introduction in the early 1990s.

(2) Evolution has a firm place as a foundational science in biomedicine, largely because of descriptive genetic and phylogenetic approaches. These are generally identified by the NLM MeSH term **Phylogeny**. Many of these phylogenetic approaches have flourished over the last two decades and have recently adopted the "evolutionary medicine" label.

(3) Adaptation and natural selection have been the focus of many publications in evolutionary medicine. Compared to **Phylogeny**, the MeSH terms **Adaptation, Biological** and **Selection, Genetic** are mapped to fewer publications and show a smaller rate of growth, although they are more likely to yield citations that are relevant to evolutionary medicine.

(4) Limitations of existing subject identifiers in PubMed make it harder than necessary to identify publications related to evolution in health and disease. The growth in the numbers of conferences, named academic centers, and publications focused on evolutionary medicine provide a strong argument for a new MeSH term for evolutionary medicine.

Acknowledgments The author appreciates Jon Eldredge, Philip Kroth, Dorothy Vanderjagt, and two reviewers for their invaluable help with this manuscript.

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