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Research Article

Paleoparasitology and paleopathology. Synergies for reconstructing the past of human infectious diseases and their pathocenosis

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ABSTRACT

Paleopathology, a discipline studying human and animal diseases of the past, developed at the beginning of the 20th century. In 1910, the father of the discipline, Sir Marc Armand Ruffer, was the first paleopathologist to describe a human parasitic disease; urinary shistosomiasis on Egyptian mummies dating from the Dynastic period. Therefore, paleopathology and paleoparasitology have the same roots. However, since the beginning, these two fields did not evolve at the same scale, as the demography of paleopathologists, combined with that of anthropologists, increased much faster than the community of paleoparasitologists. On the other hand, since the last decade, a new field, paleomicrobiology, uses molecular techniques to identify ancient pathogen DNA. This approach has mainly been applied to bacterial pathogens, such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Yersinia pestis*, *Rickettsia prowazecki* and *Bartonella quintana*, due to the fact that anthropologists and paleopathologists are, for the moment, the main specialists dealing with molecular biologists. As the past human microbiological world should be considered as a whole, according to the concept of pathocenosis, it is time to establish a synergic link between paleoparasitology and paleopathology in order to significantly increase our knowledge of past human infections.

1. Introduction

The best definition of Paleopathology remains the first, formulated in 1913 by Sir Marc Armand Ruffer, who carried out pioneering work in this field. He introduced paleopathology as "the science of diseases which can be demonstrated on the basis of human and animal remains" (Ruffer, 1913:149). Ruffer started his career in paleopathology in Egypt, by conducting intensive research on Egyptian mummies from all periods.

To gain a better understanding of how Ruffer became interested in this field, it is worth recounting some aspects of his life (Sandison, 1967). Born in France in 1859 of a French father, the baron Alphonse-Jacques de Ruffer, Marc Armand became a British citizen, due to his secondary British education and medical studies accomplished at University College, London. Back in France, he was one of the first disciples of Louis Pasteur at the Pasteur Institute, at its very beginning. He then decided to specialize in the new rapidly developing science of microbiology. In 1891, he returned to London and was named the first director of the British Institute of Preventive Medicine, later to become the Lister Institute. Unfortunately, he was to become a victim of his research. While testing new antisera for diphtheria, he was so severely paralyzed by the toxin that he decided to resign his directorship. He then went to Egypt to recover his health. He settled in Ramleh and became Professor of Bacteriology at the Cairo School of Medicine. There he developed a growing interest in studying diseases on Egyptian mummies. The years 1910–1913 were decisive for the discipline, as Ruffer published the first paleopathological diagnosis of bilharziosis, by identifying *Schistosoma bilharzia* eggs in mummy kidneys (Ruffer, 1910) and his definition of paleopathology as a new science (Ruffer, 1913). Unfortunately, Ruffer did not live long enough to publish his body of work in paleopathology. In the spring of 1917, while returning to Egypt from Salonika, where he was in charge of the reorganization of the Greek sanitary service, he drowned at sea when his ship was torpedoed by a German submarine. After his death, his wife and his colleague Roy Moodie published in 1921 his major scientific contribution to paleopathology in a collected volume edited by Moodie and entitled "Studies in the Palaeopathology of Egypt" (Ruffer, 1921). The manner in which Ruffer could have developed his disciplinary concepts in paleopathology therefore remain unknown, but we can speculate that his first center of interest in microbiology and infectious diseases that he started at the Pasteur Institute would have influenced his body of work, particularly concerning the study of parasites on ancient Egyptian material.

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2. Paleopathology and paleoparasitology as "sister" sciences

One can consider that paleopathology and paleoparasitology have the same roots, as they are known to have the same 'father', who is Marc Armand Ruffer.

Ruffer can indeed be considered as the real father of paleopathology. Shufeldt, who invented the neologism before Ruffer, did not display global multidisciplinary vision when he presented his neologism: "the word used in the title of this paper is a term here proposed under which may be described all diseased or pathological conditions found fossilized in the remains of extinct or fossil animals" (Shufeldt, 1893:679). Moreover, this short note, devoted to the description of some pathological conditions that Shufeldt observed on bones of ancient North American birds (for his main interest was ornithology), was his only contribution to paleopathology.

Some other authors proposed subsequent definitions, which minimized, consciously or not, Ruffer's original contribution to paleopathology. By presenting paleopathology as the "science of ancient diseases", these definitions emphasize chronological issues, therefore presenting a simplistic point of view. For instance, Møller-Christensen (1972), when proposing osteo-archeology as a new discipline, wrote: "Paleopathology has for many years been one of the fundamental disciplines of the history of medicine. The word 'paleopathology' means literally: the science of very ancient diseases. Due to the fact that we have no contemporary literary reports about diseases in prehistoric men and animals, we only can find information about this important subject by studying skeletons. Prehistoric skeletons can be difficult to date, and often their state of preservation is so bad that the diagnoses of the diseases are dubious, and sometimes it is pure guesswork. This is – in short – the contents of the research with the limited possibilities and uncertain scientific results which are characterized as paleopathology" (Møller-Christensen, 1972:411).

Therefore this author proposed the term "osteo-archaeology" instead of paleopathology, which he considered incorrect for naming the study of pathological conditions on skeletons postdating prehistoric periods. This neologism "osteo-archaeology" has (at least) four meanings all rolled into the same word, as it defines, according to Møller-Christensen (1972): (i) a specific method for excavating skeletons dating from historical periods, (ii) a way for constituting skeletal collections specifically adapted to pathological studies, (iii) results from these studies and (iv) an "auxiliary science" of the History of Medicine. As the 'osteo-archaeological' method of excavating, as described in this paper, can no longer be accepted by modern funerary archeologists and anthropologists, this obsolescence of the so-called "osteo-archaeological" method renders the other meanings of this term questionable. Caution should therefore be applied today when using this word as synonymous or equivalent to paleopathology (Dutour, 2011).

Restricting paleopathology chronologically to the study of ancient diseases is far from Ruffer's view, which defined paleopathology as an integrative discipline and did not introduce any chronological or methodological divisions or limitations. That is why the pioneering role played by Ruffer is indisputable, for it was he who actually set up research objectives in the field of paleopathology. This issue is, according to Ortner (2011), a critical basic question for paleopathology, as for any scientific discipline. Indeed, the objective assigned to paleopathology by Ruffer is to identify diseases on the basis on ancient remains, human or animal, whatever the methods used and the period concerned. This means that paleopathology adopts a holistic approach (even if Ruffer never used this word in his definition) and works within a multidisciplinary framework.

Therefore all scholars from biological/medical sciences or from social sciences and humanities with a scientific interest in past diseases can contribute to global paleopathological knowledge, whatever their specialty. This comprehensive view confirms the validity of Ruffer's definition, even with the recent development of new analytical methods, such as next generation sequencing and metagenomics.

As Ruffer was also the first to identify parasitic disease in ancient human remains, he is also appropriately considered a founder of paleoparasitology. Sandison validated this idea in his paper paying tribute to Ruffer's contribution to paleopathology: "Perhaps the most important was his discovery of the calcified eggs of *Schistosoma haematobium bilharzia* in the straight tubules of the kidneys of two twentieth dynasty Egyptian mummies [. . .]. This observation is of cardinal importance since it extends back the history of schistosomiasis for three millennia and substantiates the statements in the great medical papyri from ancient Egypt that haematuria was common. I suppose this might be regarded as the foundation of a new science of paleoparasitology [. . .]" (Sandison, 1967:152).

However, as Ruffer was not the author of this term and because his premature death did not leave him enough time to develop his concepts in terms of disciplinary issues, we cannot speculate on his willingness to make – or not – paleoparasitology a separate discipline alongside paleopathology or a subfield of it. The founder of the Paleopathology Association, Aidan Cockburn, pointed out the importance of studying intestinal parasites in human coprolites (Cockburn, 1967). Ferreira et al. (1979) named this approach paleoparasitology, and considered it as a new field of science (Ferreira et al., 1993; Gonçalves et al., 2003). Araújo et al. (1981), consider paleoparasitology a research field within paleopathology, studying parasitic remains from both archeological and paleontological contexts. Reinhard (1990, 1992) suggested that the word paleoparasitology should rather be applied to studies of nonhuman, paleontological parasitic remains, as 'paleo' refers to ancient paleontological times and proposed the name "archeoparasitology" or "archeological parasitology" for the study of parasitism among humans and domesticated animals, based on the analysis of remains of parasites from archeological contexts. In this view, archeoparasitology is a multidisciplinary field within paleopathology whereas paleoparasitology is a subfield of paleontology. This terminological distinction in the study of parasitism in the past is justified in terms of trends and distinct goals: paleoparasitology focuses on the evolution of parasite biogeography and archeoparasitology deals with the cultural ecology of parasitism in relationship to human activity. Concerned that this distinction could overly emphasize, mainly for scholars and students from other disciplines, the difference between the two, cohesive reviews have been recently presented (Dittmar et al., 2012).

If paleopathology and paleoparasitology (in its broadest sense) can be considered as "sister sciences", as they have the same paternity, they grew up differently. A swift bibliometric survey (Web of Sciences) using the two key-words revealed that the key-word 'paleopathology' is used by about 500 scholars; publishing their articles in various journals (20% of the papers are published in the *American Journal of Physical Anthropology*) and showed that 45 books (textbooks or research books) deal with this topic. Under the key-word "paleoparasitology" there are fewer than 50 scholars; publishing 50% of their research in one Journal (*Memorias Instituto Oswaldo Cruz*); and one textbook has been recently published in Brazil (Ferreira et al., 2011). This statistical discrepancy might be due to the fact that paleopathology was associated at an earlier stage with anthropology and recruited many scholars from this large scientific community; where paleopathology is taught as a branch of physical anthropology. The scientific community of paleoparasitologists appears to be smaller; mostly originating from archeological; environmental or biomedical sciences;

with paleoparasitology is principally taught in these disciplinary fields.

It should be mentioned that two recent (text)books in paleopathology (Grauer, 2012; Buikstra and Roberts, 2013) underlined the study of ancient parasites as an approach in paleopathology (Dittmar et al., 2012; Reinhard and Araújo, 2013). This might encourage more students in anthropology and archeology interested in paleopathology to specialize in the study of ancient parasites or it possibly persuade scholars in biological anthropology and paleopathology to gain additional skills in this area. Increased numbers of specialists studying different aspects of the past host–parasite relationships would reduce the differential development of these two sisters disciplines. Other synergistic relationships could be established thanks to recent advances in molecular biology applied to ancient remains.

3. Paleomicrobiology as a new arrival

In the 90s, the development of molecular biology techniques made it possible to detect and amplify small fragments of DNA still preserved in ancient material, including human bones and mummified tissues (Hagelberg et al., 1989; Hänni et al., 1990; Pääbo, 1993; Herrmann and Hummel, 1994). Thus significant new results were obtained about ancient human pathogens. During the next two decades, the number of identifications of human pathogens on ancient human material increased dramatically (Zink et al., 2002), including the detection of *Mycobacterium tuberculosis* (Spigelman and Lemma, 1993), *Mycobacterium leprae* (Rafi et al., 1994), *Plasmodium falciparum* (Taylor et al., 1997), *Influenza virus* (Taubenberger et al., 1997), *Trypanosoma cruzi* (Guhl et al., 1997; Aufderheide et al., 2004), *Yersinia pestis* (Drancourt et al., 1998), *Treponema pallidum* (Kolman et al., 1999), HTLV-1 (Li et al., 1999), *Human papillomavirus* (Fornaciari et al., 2003), *Bartonella quintana* (Drancourt et al., 2005), *Rickettsia prowazecki* (Raoult et al., 2006). This molecular approach was applied to medieval human coprolites, leading to the first identification of the ancient DNA of *Ascaris lumbricoides* and *Enterobius vermicularis* (Loreille et al., 2001). The interest in detecting the molecular signature of infections caused by bacteria, viruses and parasites of ancient remains has been emphasized by Drancourt and Raoult (2005) and Raoult and Drancourt (2008), who named this emerging field "Paleomicrobiology". Besides protozoan parasites, such as *Plasmodium* and *Trypanosoma*, that can be referred as microbes *sensu lato*, Drancourt and Raoult (2008) listed helminth species such as *Ascaris* and *Enterobius* as parasites belonging to the field of paleomicrobiology (Drancourt and Raoult, 2008, Table 4.3, p. 63). Other authors named "molecular paleoparasitology" (Araújo and Ferreira, 2000; Araújo et al., 2003) or "molecular based paleoparasitology" (Dittmar, 2009) the study of parasites using molecular techniques on ancient human remains, including bones, tissues and coprolites. Ancient ectoparasites (fleas or lice) can benefit as well from this molecular approach in paleoparasitology (Dittmar et al., 2003; Raoult et al., 2006, 2008).

It should be noted that the word 'Paleomicrobiology' is not a new one, as it was used in 1969 (Swain, 1969) to describe the morphological study of prokaryotic micro-organisms, fossilized in Precambrian, Devonian and Eocene sedimentary rocks. However, it is the new definition of paleomicrobiology that is now popular among scholars, considered as an original approach "at the intersection of microbiology and evolution, history and anthropology" that allows "looking backwards to past epidemics using modern tools and concepts" and that "will in turn help to understand the continuous evolution of microbes and of their direct or indirect relationships with humans" (Raoult and Drancourt, 2008: v).

Besides the identification of these pathogens, molecular studies also creates new possibilities for reconstructing their evolution, as it can contribute to a better understanding of emerging infections.

The complete reconstruction of the genome of ancient pathogens now appears to be attainable, thanks to the development of metagenomics and its application to ancient living organisms, called paleogenomics (Poinar et al., 2006). The first application of this method has been published recently for the Black Death pathogen, *Y. pestis* (Bos et al., 2011) and more recently for *M. tuberculosis* (Chan et al., 2013). Dittmar (2009) underlined that genomics can also be used to better understand life history traits of ancient and extant parasites, but so far no genome of parasites identified in ancient material have been published.

In very near future this will bring fantastic new opportunities for grasping a clear knowledge of the origin, dispersal, pathogenicity and virulence of pathogens in the past. If the term "paleomicrobiology" does not fully encompass this field, because it could be understood *sensu stricto* and then exclude multicellular (endo and ecto) parasites, then a new term should be coined to bring together all molecular based studies of pathogens in the past, as host–pathogen relationships should be conceived as a whole, in an ecological continuum.

4. Human–pathogen relation as a whole

The number of known human pathogens is now 1407, according to Woolhouse and Gowtage-Sequeria (2005). Bacteria rank first (38%), parasites second (24%), fungi third (23%) and viruses fourth (15%). Among these pathogenic species, about 177 are responsible for emerging or re-emerging infectious diseases (Woolhouse and Gowtage-Sequeria, 2005) that can be defined as: "An infectious disease whose incidence is increasing following its first introduction into a defined host population, or an infectious disease whose incidence is increasing in a defined host population as a result of long term changes in its underlying epidemiology" (Woolhouse and Dye, 2001). Viruses and prions are taking the lead in emerging or re-emerging pathogenic species (44%), bacteria in second, and fungi and parasites are third (13%).

Numerous environmental and social factors influence the emergence and re-emergence of infectious diseases (McMichael, 2004). Besides travel and trade, human-induced environmental changes due to land use have been ranked according to their decreasing level of influence on emerging diseases (Patz and Confalonieri, 2005). These include: agricultural development, urbanization, deforestation, population movement, introduction of species/pathogens, reduction of biodiversity, habitat fragmentation, and water and air pollution. Six main ecological disruptions related to human activities are responsible for the emergence of infectious diseases (McMichael, 2004): altered habitat with proliferation of reservoir or vector populations, biodiversity change and habitat fragmentation, ecosystem changes and loss of predators, intensified farming and animal husbandry, niche invasion and host transfer. The human–pathogen relation must thus be understood in a broader ecological and evolutionary framework.

Reinhard introduced in 1974 the concept of "pathoecology" in the study of environmental influences (including both social and natural factors) on the development of diseases conditions and applied it to parasitology (Reinhard, 2007, 2008). Reinhard and Bryant recently proposed (2008) to introduce in bioarchaeology the concept of "nidality", previously developed for infectious diseases by Pavlovsky (1966). According to this author, the "nidus" of a disease exists under "definite conditions of climate, vegetation, soil, and favorable microclimate where pathogens, vectors, and reservoirs are associated as a biocenose that is characteristic for a definite geographic landscape". Therefore, man can acquire a "animal natural–nidal disease" when he penetrates or occupies at a given time the biocenose of that infection (Pavlovsky, 1966:9).

According to Woolhouse and Gowtage-Sequeria (2005), 58% of human pathogens are zoonotic which means that we share pathogens with a wide range of other animal hosts. As pathogens can have multiple hosts they therefore have to share their hosts as well. If the host is changing in response to one pathogen, this change can also affect its response to other pathogens. Pathogen jumps between host species are frequent and interactions between pathogens within the same host can affect their epidemiology and evolution by facilitation, inhibition or cross-immunity. For instance, helminth infections affect the balance between lymphocytic T-cell types and consequently increase host susceptibility to other infections. A more comprehensive approach has to be developed, far from the "single pathogen, single host, single disease" simplistic model. The human–pathogen relation appears to be very complex and corresponds more to a multi-host–multi-pathogen biological model (Woolhouse and Gowtage-Sequeria, 2005). This concept has been clearly adopted for past pathogens by Raoult and Drancourt (2008) and Dittmar (2009), among others.

Recently, Singer (2010) reviewed the different mechanisms of pathogen interactions and introduced the concept of epidemiological synergism and syndemism for defining the biological interactions between pathogens, which influence their speed, spread and virulence.

This holistic approach to disease ecology was previously defined by Mirko Grmek, paleopathologist and medicine historian, termed "pathocenosis" (Grmek, 1969). He proposed to consider diseases of a given host population as a whole, thereby integrating historical and geographic dimensions. He named this concept by analogy with the ecological concept of "biocenosis", which globally considers all living organisms coexisting and interacting within a defined territory. Grmek defined pathocenosis as follows: "By pathocenosis, I mean the qualitatively and quantitatively defined group of pathological states present in a given population at a given time. The frequency and the distribution of each disease depend not only on endogenous—infectivity, virulence, route of infection, vector—and ecological factors—climate, urbanization, promiscuity—but also on frequency and distribution of all the other diseases within the same population" (Grmek, 1969:1476). According to Gonzalez et al. (2010), this was the first time in the history of medicine that a scholar proposed a temporal and spatial approach for understanding the dynamics of infectious diseases and their interdependency, rather than keeping diseases "in a frozen disciplinary framework" (Gonzalez et al., 2010:238).

5. In conclusion, Darwin, as always

Darwin, 20 years before publishing his revolutionary book, confirmed an example of a human–pathogen relationships that was noted in Australia in 1837 by the English missionary John Williams, and quoted: "It is certainly a fact, which cannot be controverted, that most of the diseases that have raged in the islands during my residence here, have been introduced by ships; and what renders this fact remarkable is that there might be no appearance of the disease among the crew of the ship which conveyed this destructive importation..." (Darwin, 1839 in the Voyage of the Beagle: 521). This observation finds later its immunological explanation in terms of epidemiological isolate.

In spite of this observation, Darwin did not introduce germs and infectious diseases into his evolutionary model twenty years later, even if he must have been aware of the research of his contemporaries, Pasteur and Koch.

However, the history of human pathogens is intimately inscribed in the evolutionary paradigm that Darwin scientifically introduced in its modern form in 1859. Darwin's prescient model, capable of explaining, extinction, emergence and re-emergence, as well as multidrug resistance in the field of human infectious diseases, thus created a scientific model for understanding the modern history of certain pathogens (Iseman, 2007). On the basis of this strong paradigm, it has been possible to build the model of co-evolution (Ehrlich and Raven, 1964), clearly illustrated by the Reed Queen Theory (Van Valen, 1973), very useful for understanding host–pathogen interactions. Modern examples of emerging and remerging diseases, such as tuberculosis, HIV, SARS, Mad cow disease, Western Nile fever, Rift Valley fever, Ebola fever, H5N1 & H1N1 flu, Lyme disease, Chikungunya... among others, have demonstrated that these interactions have to be understood within the time scale, in a global ecological framework.

It is now time, in these changing scientific environments, that all specialists of sciences concerned with the past interested in human diseases find, like some of the studied pathogenic species they are studying, new synergies. Whatever their variable background, disciplinary framework, and origins (either from biological and health sciences or from social sciences and humanities), they must follow this holistic perspective inspired by Darwin's ideas, in order to be able to clearly understand, as an essential adaptation feature for scientific survival, the past of human infections.

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