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# Émile Littré and the death of Alexander the Great: a Philological and Medical Reappraisal

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**ABSTRACT** The French medical philologist Émile Littré (1801-1881) is credited by several scholars as the first to propose that Alexander the Great died of malaria. This article demonstrates that this opinion of traditional origin is unsupported by Littré's scholarly production. He published only two full papers on the topic of Alexander's death, the first in 1844 and the latter in 1853. In both works he stated that Alexander died of a pseudo-continuous fever, that is, a long-lasting fever characterized by initial phases of remission to become continuous at the end. This feverish pattern differed from that of intermittent fever of malarial type that Littré described in his medical Dictionary. The articles of 1865, 1872 and 1927 were purely reprints of the 1853 article. The 1927 version published in *Æsculape* was preceded by a preface in which the anonymous author arbitrarily introduced the new word "paludisme", giving rise to the erroneous belief that has been handed down to date.

**KEYWORDS** Émile Littré, Alexander the Great, malaria hypothesis, pseudo-continuous fever.

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Nowadays, the death of Alexander the Great (356-23 BCE) remains the object of much debate, and there is a wide heterogeneity of opinion concerning causes of death<sup>1</sup>. Although it is fair to conclude that in the absence of Alexander's corpse ancient sources are not sufficient to establish the cause of death with certainty<sup>2</sup>, over time infectious diseases, and in particular malaria<sup>3</sup> and typhoid fever<sup>4</sup>, have established themselves as the most convincing diagnostic hypotheses to explain Alexander's unexpected death. Concerning the "typhoid fever hypothesis", one of the main arguments in support is that, historically, during military campaign disease losses have always exceeded combat casualties<sup>5</sup>. Among infectious diseases, typhoid fever has been one of the most

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<sup>1</sup> For a detailed bibliography of this topic, see DAMIANI 2012; DAMIANI–ELICE–PECA CONTI 2021.

<sup>2</sup> ANTELA-BERNÁRDEZ–SIERRA MARTIN 2018, 39 n. 31, "the sources do not allow us, in our opinion, to argue what illness exactly was"; SALLARES 2002, 11, "biographical accounts of the illnesses of individuals, such as Alexander the Great, frequently provide too little detail for a reliable retrospective diagnosis".

<sup>3</sup> RADET 1931; BERTELOTTI 1932; DESTAING 1970; MOULOPOULOS 1998; CILLIERS–RETIEF 1999; 2006. For a detailed discussion on malaria as the possible cause of Alexander's death, see DAMIANI 2012, 85-133 (Chapter IV).

<sup>4</sup> OLDACH 1998a; 1998b; BORZA 2000; CUNHA 2004; HALPERIN 2006; CUNHA 2007; DAMIANI 2012; DAMIANI–ELICE–PECA CONTI 2021.

<sup>5</sup> OLDFIELD III–WALLACE–HYAMS–YOUSIF–LEWIS–BOURGOIS 1991.

dangerous<sup>6</sup>, until the introduction of mandatory vaccination for soldiers during WWI. Malaria also impacted on wars<sup>7</sup>, but it is now known perfectly that malaria and poverty are intimately connected<sup>8</sup>, and therefore its possible impact on ancient civil societies has been debated for a long time now<sup>9</sup>. In recent times, using a multidisciplinary approach Robert Sallares et al. convincingly argued that malaria caused *P. falciparum* affected health, prosperity, and settlement patterns in the ancient Roman world<sup>10</sup>. These conclusions are shareable, since the different types of malaria fevers (benign tertian, benign quartan, malignant tertian) had been clearly described long since by the Latin author Aulus Cornelius Celsus (25 BCE-45 CE)<sup>11</sup>. Furthermore, in 1890 the Italian physicians Angelo Celli (1857-1914) and Ettore Marchiafava (1847-1935) had already demonstrated that *P. falciparum* was the parasite responsible for the “aestivo-autumnal” tertian fevers observed in Rome<sup>12</sup>. Regarding the possibility of generalizing these conclusions to the Mediterranean ancient world, Sallares et al. correctly pointed out that “malaria did not occur everywhere” and that “malaria had considerable effects in Mediterranean Europe in antiquity only at a localized effect”<sup>13</sup>.

One of the most common errors in historical research is the use of tralatitious information, that is, of “traditional origin” (from the Latin *traditus*, handed down), passed along from generation to generation in written or oral form without verifying the sources. Concerning the “malaria hypothesis” for the death of Alexander, an example of tralatitious information is the claim by some scholars that the French medical philologist Émile Littré (1801-1881) first proposed this malady as the one that killed the young Macedonian king.

Littré was a distinguished figure in the French cultural landscape of the nineteenth century<sup>14</sup>. A major exponent of Positivism<sup>15</sup>, he was author of a five-volume *Dictionnaire de la langue française* (also known as *Dictionnaire Littré*), defined as a “gigantic accomplishment” by the American medical historian Fielding H. Garrison (1870-1935). Littré’s work was equally relevant for the History of Medicine<sup>16</sup>. The Italian historian of medicine Arturo Castiglioni defined Littré “a philologist, who was

<sup>6</sup> CONNOLLY–HEIMANN 2002. GRADMANN–HARRISON–RASMUSSEN 2019. See also CONAN DOYLE 1900, 370-371, in which the Scottish writer and physician, who was voluntarily serving at the Bloemfontein Hospital in South Africa during the *Second Anglo-Boer War* (1899-1902), reported on an epidemic of typhoid fever that caused 57,684 cases with a mortality of 13.9%. The very same happened during the *Spanish-American War*, in which a typhoid fever epidemic lasting from July to November 1898 killed 1,590 soldiers with a mortality rate of 7.7%: CIRILLO 2000.

<sup>7</sup> MERTENS 2024.

<sup>8</sup> GALLUP–SACHS 2001.

<sup>9</sup> For a discussion on this topic, see SALLARES 2002; SALLARES–BOWMAN–ANDERUNG 2004.

<sup>10</sup> SALLARES–BOWMAN–ANDERUNG 2004. See also the monography published by Sallares in 2002, containing much more bibliography on the question considered in the journal article.

<sup>11</sup> In *De Medicina*, Celsus (Cels. 3.3) described three types of fevers, “one is Quotidian, another Tertian, and a third Quartan... The quartan fevers begin, generally, with shivering, then a heat breaks out; and the paroxysm being over the patient is free for two days: and thus, it returns on the fourth days... There are two kinds of tertian. The one hath beginning and terminating like the quartan; with this distinction only, that there is one clear day, interposing, and returning on the third. The other is by far more dangerous because it returns indeed on the third day, but out of forty-eight hours, it occupies thirty-six of these in the paroxysm, sometimes less or more; nor does it cease entirely in the remission, but is only mitigated. Most physician call that genus semitertian”, (transl: LEE 1831, 151-152).

<sup>12</sup> CELLI–MARCHIAFAVA 1890a; 1890b.

<sup>13</sup> SALLARES–BOWMAN–ANDERUNG 2004, 312.

<sup>14</sup> For a complete biography and a selected bibliography of Littré’s works, see AQUARONE 1958.

<sup>15</sup> See HEILBRON 2007, for a detailed bibliography of Littré’s works on Positivism.

<sup>16</sup> For a survey of the medical works of Littré, see DAREMBERG 1882, 634-671.

a pioneer and an apostle in the field of medical history”<sup>17</sup>. Although he never obtained the degree of doctor<sup>18</sup>, Littré had a vast knowledge of medicine that led him together with Charles Robin (1821-1885)<sup>19</sup> to entirely recast in 1855 the tenth edition of a very popular *Dictionnaire de Médecine*<sup>20</sup>. Furthermore, thanks to his mastering of Greek and other ancient and modern languages, Littré published a complete bilingual edition of *Corpus Hippocraticum* in ten volumes, which still forms the most important reference book for Hippocratic literature<sup>21</sup>. For his merits in 1858 he was honored with a membership of the French Academy of Medicine.

The suggestion that Littré proposed malaria as the fatal disease of Alexander the Great was originally put forward in 1978 by Donald Engels<sup>22</sup>. In his words, “as early as 1872 the great French physician Emile Littré noted that Alexander’s symptoms before his death did not resemble those caused by poisoning but were very similar to symptoms caused by a pernicious manifestation of *Plasmodium falciparum* malaria”. Since then, Engels’s statement has been repeated times and again<sup>23</sup>.

This conclusion, however, seems puzzling because during Littré’s lifetime malaria did not even exist as a disease *sui iuris*. The term *malaria*, coming from “mal’aria”<sup>24</sup>, meaning literally “bad air,” had been introduced in current learned language of eighteenth century by the aristocratic English writer Horace Walpole (1717-1797)<sup>25</sup>. The word stemmed from the supposed miasmatic origin of the disease. The etiological agent of malaria, a protozoan parasite belonging to the *Plasmodium* genre, was discovered by French physician Alphonse Laveran (1845-1922) only in 1880 in the blood of sick people and named by him *Oscillaria malariae*<sup>26</sup>. After Laveran’s discovery, the further clarification of the biology of malarial parasites and their relationship with malarial fevers stands out as a glory of Italian medicine<sup>27,28</sup>. In 1885, Marchiafava and Celli coined the name of *Plasmodium*, by which the malarial parasite

<sup>17</sup> CASTIGLIONI 1948, 639.

<sup>18</sup> LITTRÉ 1872, 1-2: “J’ai vécu dix ans dans les hôpitaux comme externe, comme interne, comme disciple assidu à la visite de M. Rayer, et cependant je n’ai passé aucun examen, n’ai aucun titre médical et ne suis pas docteur”.

<sup>19</sup> It is interesting to note that it was Emile Littré who introduced Charles Robin to Comte and positivism (THOMAS 2020, 267), and that Robin represented the French resistance to the cellular theories of German biologist, see LOISON 2015.

<sup>20</sup> LITTRÉ 1855. Starting from the fourteenth edition of 1884, the dictionary included only the name of Littré.

<sup>21</sup> LITTRÉ 1839-1861.

<sup>22</sup> ENGELS 1978.

<sup>23</sup> SALLARES 1991, 273: “Littré (1872) concluded that Alexander the Great died from an attack of malaria at Babylon”; LIAPPAS–LASCARATOS–FAFOUTI–CHRISTODOULOU 2003, 562: “Based on this information [the Royal Diaries], the great Hippocraticist, Littré (1865) propounded the view that Alexander died as a result of malaria”; RETIEF–CILLIERS 2006, 25-26, “the fact that Alexander’s symptoms resemble those of malaria, was noted as early as 1872 by the French physician Emile Littré”; CHUGG 2007, 31 n. 58: “The French physician, Emile Littré, diagnosed Alexander’s fatal illness as falciparum malaria in *Médecine at Médecins*, Paris, 1872, pp. 406-415”; STAHULJAK 2013, 148: “Littré argued that it was not poison that killed Alexander, but ‘intermittent fever’, or malaria”.

<sup>24</sup> CROTTI 2005, 266, suggested that the term *mal’aria*: originated in Venice in 1571.

<sup>25</sup> Walpole first cited “*mal’aria*” in a letter dated July 5, 1740 written to a friend from Radicofani (Tuscany): “There is a horrid thing called the mal’aria, that comes to Rome every summer, and kills one”: WRIGHT 1840, 48.

<sup>26</sup> LUZI 2021, 9.

<sup>27</sup> BRUCE–CHWATT–DE ZULUETA 1980: “The Italian contribution in this field is immense”. For the contribution of Italian scientists to the discoveries that established the role of *Plasmodia* and *Anopheles* mosquitos in malaria, see ASCENZI 1999; LUZI 2021.

<sup>28</sup> For a general history of malaria, see PACKARD 2021.

is known today<sup>29</sup>. They also clarified that the malignant tertian fever occurring in Italy during the summer-autumn period was a disease distinct from the benign tertian observed during springtime. In 1886, Camillo Golgi (1843-1926), later a Nobel laureate<sup>30</sup>, studying the blood of sick people living around the rice fields of Pavia in northern Italy demonstrated that the parasite reproduced by sporulation, that the febrile paroxysm coincided with the liberation of spores and that parasites of quartan and benign tertian were morphologically different, that is, *P. malariae* and *P. vivax*<sup>31</sup>. In 1889, he also established the relation between hemolysis and febrile paroxysms. In a series of works published from 1898 to 1899, Giovanni Battista Grassi (1854-1925), Amico Bignami (1862-1929) and Giuseppe Bastianelli (1862-1959) described the development of malaria parasites in female *Anopheles* mosquitos, whose role in the transmission of the disease was conclusively demonstrated by Ronald Ross (1854-1932), working in India, and by Grassi, working in Italy<sup>32</sup>.

Given these premises, the claim that Littré was the father of a “malaria hypothesis” for explaining Alexander’s death seems anachronistic. Based on a careful analysis of Littré’s literary production about Alexander’s death, this article demonstrates that this belief is completely unsupported.

### Littré’s first work of 1844

Littré published his first note on Alexander’s death twenty-eight years earlier than Engels’ claim, in 1844<sup>33</sup>. It was a six-page text, the excerpt of a “mémoire inédit” on the last illness of Alexander printed as an appendix to an edition of Plutarch’s *Vie d’Alexandre* published by the Swiss philologist Louis de Sinner. To the best of my knowledge, this work of Littré has never been cited in the modern international scientific literature<sup>34</sup>. At that time Littré was deeply involved in editing *Corpus Hippocraticum*. In fact, in 1844 the first four volumes of this *opus magnum* had already been published. For this very reason de Sinner dedicated this edition of Plutarch’s work to Littré. The importance that de Sinner attributed to Littré’s text can be deduced from the “Avertissement” to the text, in which de Sinner said: “nous avons préféré donner moins de notes afin de pouvoir gagner assez de place pour communiquer à nos lecteurs le résumé substantiel de la seconde partie d’un Mémoire inédit sur la dernière maladie et la mort d’Alexandre, que M. E. Littré a bien voulu nous confier”.

The interest of Littré for the subject of Alexander’s death does not surprise, since he was also a pioneer in the field of “medical history”<sup>35</sup>. The span of years around the mid-nineteenth century represented the moment in which medical history, that is, the

<sup>29</sup> SABROSKY–USINGER 1944.

<sup>30</sup> For the role of Camillo Golgi on malaria studies, see SIMIO–CODREANU–CORLATESCU–PAUNA–CILIEVIVI 2023.

<sup>31</sup> GOLGI 1886. The article represents the written transcription of a memory presented to the Royal Academy of Medicine of Turin on November 15, 1885.

<sup>32</sup> See ASCENZI 1999, for the complete biography of these works.

<sup>33</sup> LITTRÉ 1844.

<sup>34</sup> The only reference to this text can be found in BERTOLOTTI 1932, 398 n. 1: “Nella Edizione Sinneri della ‘Vita di Plutarco’ (Parigi 1842), a p. 133 Littré scrisse un interessante commento dal quale stralciamo il brano seguente: Alexandre, quoi qu’on dit, n’est pas mort du poison mais de la fièvre; la fièvre à la quelle succomba est la fièvre continue ou pseudo-continue des pathologistes des pays chauds; ou bien encore, si nous tenons dans la pathologie antique, c’est la fièvre sinèque, ξ□□□χής d’Hippocrate”.

<sup>35</sup> STAHULJAK 2013, 149.

historical study of medicine, began to take shape as a modern, scientific discipline distinct from medicine<sup>36</sup>. In the words of Nicolas Rupke, “by the middle of the nineteenth century, medical historiography took a sharp turn, when various medical reforms led to placing of medical education on a scientific footing”<sup>37</sup>. These reforms were: 1) the “cell theory”, formulated in 1838 by the botanist and physician Matthias Jacob Schleiden (1804-1881)<sup>38</sup>. According to this theory, plants were formed by aggregations of microscopic, independent units, the cells in fact; 2) the generalization of the “cell theory” to all living beings. In a most famous book published in 1839, the German physician Theodore Schwann (1810-1882) stated that all plant and animal tissues are made of cells<sup>39</sup>; 3) the “cellular pathology theory”, proposed in 1858 by the “the hero of pathology”<sup>40</sup>, the German physician Rudolf Virchow (1821-1902), according to whom diseases were to be interpreted as the consequences of structural and functional alterations of the cells<sup>41</sup>. With the “cell theory” the cell had become the elementary form of every living being; with the “cellular pathology” the cell had become the elementary patient. Because of these scientific developments, “contemporary medical knowledge was no longer uncritically equated with the sum total of the classic literature from the past”<sup>42</sup>. By the time Littré published in 1861 the tenth and final volume of his edition of *Corpus Hippocraticum*, “Hippocrates and Galen had stepped out of medicine and into history”<sup>43</sup>.

The first example<sup>44</sup> of this new genre of medical history was *An excellent history of medicine*<sup>45</sup> published in 1859 by Carl A. Wunderlich (1815-1877)<sup>46</sup>, he himself an authoritative protagonist of the scientific revolution in medicine for his treatise on clinical thermography that changed fever from a disease to a symptom. In France, in 1870 Charles Daremberg (1817-1872), “the ablest medical historian of France”<sup>47</sup>, published a *Histoire des sciences médicales*<sup>48</sup>, that “remains today an extremely useful work and, moreover very pleasant to read”<sup>49</sup>. It is interesting to note, however, that Virchow refused to ignore tradition altogether, based on his consideration that observations made by ancient physicians were often correct although understandably erroneous in their interpretation<sup>50</sup>. In *Specifiker und Specifisches*, he explicitly claimed that the study of history of medicine was a research tool equivalent to all the other methods of investigative medicine:

<sup>36</sup> See RUPKE 1998-1999 for a review on evolution on history of medicine from eighteenth century up to now; GARRISON 1929 for a very detailed list of scholars and of studies of medical history from the beginning of nineteenth century up to 1929; and HUISMAN–WARNER 2004 for a more recent collection of essays examining the development of medical history towards autonomy as an academic discipline.

<sup>37</sup> RUPKE 1998-1999, 185.

<sup>38</sup> SCHLEIDEN 1838.

<sup>39</sup> SCHWANN 1839.

<sup>40</sup> MAJNO–JORIS, 2004.

<sup>41</sup> VIRCHOW 1858.

<sup>42</sup> RUPKE 1998-1999, 182.

<sup>43</sup> MAJINO 1975, 420.

<sup>44</sup> RUPKE 1998-1999, 185.

<sup>45</sup> GARRISON 1929, 430.

<sup>46</sup> WUNDERLICH 1859.

<sup>47</sup> GARRISON 1929, 665.

<sup>48</sup> DAREMBERG 1870.

<sup>49</sup> BRAUENSTEIN 2005, 386: “reste aujourd’hui un ouvrage extrêmement utile et, au surplus, fort agreable à lire”.

<sup>50</sup> VIRCHOW 1858, VI.

“Medicine needs no hostile schools, no parties fighting each other in the goal, but only competition for the same goal, at the same price, even if with different means. One may seek to advance through the anatomical examination of the patient, another through clinical observation of the processes, the third through pathological and the fourth through therapeutic experiment, one through chemical or physical research and still another through historical research: Science is big enough to allow all these directions to be recognized if they do not want to be exclusive, if they do not exceed their limits, if they do not claim to be able to achieve everything”<sup>51</sup>.

In the words of Danielle Gourevitch, “Littré and Daremberg were the two key figures of positivist medical history”<sup>52</sup>. Littré was clearly aware of developments in modern medicine, as plainly demonstrated by the fact that he was the editor of the second edition of the French translation of Johannes Müller’s *Handbuch der Physiologie des Menschen für Vorlesungen*<sup>53</sup>. Daremberg wrote that the method he used for his historical studies “was not mine; it was taught to me, more than twenty-five years ago, by a venerable, a learned master, an excellent friend, Mr. Littré”<sup>54</sup>. Daremberg left us a description of Littré’s method:

“Mr. Littré not only introduced into the history of medicine this fruitful principle of the connection of sciences, but he also eagerly welcomed that of the connection of times and the successive evolution of medicine without any interruption... Mr. Littré also applied to the entire history of medicine this beautiful method solemnly inaugurated in the interpretation of Hippocrates and which consists of carefully studying the facts previously observed with the help of the light provided by modern knowledge in anatomy, in physiology, in pathology”<sup>55</sup>.

The idea that history itself might be the object of medical analysis and that scientific developments in the field of medicine might help to solve historical puzzles developed during Littré’s lifetime as an advancement of Positivism<sup>56</sup>. Littré investigated the death of historical characters at the light of new knowledge achieved by modern medicine. He used history’s mysterious events as clinical cases for practicing medical diagnoses

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<sup>51</sup> VIRCHOW 1854, 5: “Die Medicin bedarf keiner feindlichen Schulen, keiner im Ziel sich bekämpfenden Parteien, sondern nur des Wettstreites nach demselben Ziel, um den gleichen Preis, wenn auch mit verschiedenen Mitteln. Mag der eine durch die anatomische Untersuchung des Krankhaften, der andere durch die klinische Beobachtung der Vorgänge, der dritte durch das pathologische und der vierte durch das therapeutische Experiment, einer durch chemische oder physikalische und wieder ein anderer durch historische Forschungen vorwärts zu schreiten suchen: die Wissenschaft ist groß genug, alle diese Richtungen gewähren zu lassen, wenn sie nicht exclusiv sein wollen, wenn sie nicht ihre Grenzen überschreiten, wenn sie nicht Alles zu leisten präbendiren”.

<sup>52</sup> GOUREVITCH 2004, 54. Although mainly focussing on Daremberg, this excellent study of Danielle Gourevitch investigated the relationship between Daremberg, Littré and in contemporary context as well as across Europe.

<sup>53</sup> MUELLER 1851.

<sup>54</sup> BRAUENSTEIN 2005, 372.

<sup>55</sup> DAREMBERG 1882, 658: “M. Littré n’a pas seulement introduit dans l’histoire de la médecine ce principe fécond de la connexion des sciences, mais il a aussi accueilli avec empressement celui de la connexion des temps et de l’évolution successive de la médecine sans aucune interruption”, 655; “M. Littré a aussi appliqué à toute l’histoire de la médecine cette belle méthode inaugurée solennellement dans l’interprétation d’Hippocrate et qui consiste à étudier attentivement les faits anciennement observés à l’aide de la lumière que procurent les connaissances modernes en anatomie, en physiologie, en pathologie”.

<sup>56</sup> STAHULJAK 2013.

to free history from the fairy tales that had been introduced there. In this way, “Littré’s historical studies, notably those on the great epidemics, historical suicides and poisonings set the pace for Cabanès<sup>57</sup>, and others who have followed this *genre* of historical writing”<sup>58</sup>. This was the reason why Littré became involved in studying the death of Alexander the Great, Germanicus and Britannicus, for whom the popular opinion supported death by poisoning<sup>59</sup>. He brought old questions back to life, because he wanted to analyze them in the light of the new medical knowledge.

From the very first line of the text Littré rejected the poisoning hypothesis: “Alexandre, quoi qu’on ai dit, n’est pas mort du poison, mais de la fièvre”. Concerning the type of fever responsible of Alexander’s death, Littré identified “la fièvre à la quelle il succomba comme une fièvre continue ou pseudo-continue des pathologistes des pays chauds”, corresponding to the “fièvre synèque, ξυνεχής, d’Hippocrate”. Quoting from his own edition of *Corpus Hippocraticum*, Littré described the “fièvre pseudo-continue” as a fever that “débute mollement et d’une manière lente, s’accroissant et s’exaspérant chaque jour; puis, à l’approche de la crise et pendant la crise, elle éclat dans tout son intensité”<sup>60</sup>. This type of fever differed from another type of “fièvre synèque”, that according to Hippocrates “est vive dès le début, acquiert toute sa violence et tend au plus mal, puis elle s’atténue à l’approche de la crise et au moment de la crise”<sup>61</sup>.

It is important to remind that in 1844 fever was a disease on its own right. It was the treatise on clinical thermometry by Carl Reinhold Wunderlich (1815-1877) that changed the perspective<sup>62</sup>. In the words of Fielding Garrison, “Wunderlich found fever a disease and left it a symptom”<sup>63</sup>. Wunderlich classified fevers based on the duration of the “pyrogenic phase”, that is, the phase in which the body temperature rises to reach the new “set-point” temperature fixed by hypothalamus. Based on this, Wunderlich distinguished two types of fever. The first one was characterized by a “protracted pyrogenic period” lasting several days. He described this type of fever, as follows:

“The rise of temperature generally happens thus: it begins to ascend in the evening, in the morning hours it moderates again, to rise again more the following evening. It may thus happen that the normal temperature is again reached in the morning of the second day... In this type the initial stage lasts three or four days, but seldom more than a week”<sup>64</sup>.

In addition to requiring several days to reach the *fastigium* (plateau) phase, the ascension of the body temperature was characterized by remissions of one degree Celsius or more, but always remaining above normal. Today this pattern of fever is called a stepwise remittent fever. What is most important, the presence of a protracted pyrogenic period of remittent nature attributed a diagnostic value to this pattern of

<sup>57</sup> Augustin Cabanès (1862-1928) was the most prolific writer in the field of “medical history”.

<sup>58</sup> GARRISON 1929, 667.

<sup>59</sup> According to Plutarch (*Alex.* 77.1-2), it was Alexander’s mother, Olympias, who six years after Alexander’s death began to spread propagandistic rumors that her son had been poisoned. At that time, she was fighting Antipater, and therefore she propagandistically accused Antipater’s son, Iolas, as the poisoner of Alexander.

<sup>60</sup> LITTRÉ 1844, 133. Littré quoted from his own volume: LITTRÉ 1840, 676-677.

<sup>61</sup> LITTRÉ 1844, 133.

<sup>62</sup> WUNDERLICH 1868.

<sup>63</sup> GARRISON 1929, 431.

<sup>64</sup> WUNDERLICH 1871, 246.

fever. In fact, Wunderlich stated that “this type occurs most constantly in typhoid fever, and so much that the diagnosis can be safely based upon the initial stage only”<sup>65</sup>.

On the other hand, the second pattern of fever classified by Wunderlich was characterized by a “short pyrogenic period”. He wrote: “the temperature rises suddenly and reaches the characteristic height in a few hours... Attacks of illness have for the most part but short paroxysms of fever with a sharp elevation of temperature”<sup>66</sup>. Since these fever paroxysms were separated by regular intervals of apyrexia, we call it an intermittent fever. Also, in this case thermography made possible to put forward a diagnostic hypothesis. In fact, according to Wunderlich, “this type of fever is the rule in malarial attacks”.

The comparison between the feverish patterns described by Littré and by Wunderlich, respectively, clearly allows to conclude that the “pseudo-continue” fever that took Alexander’s life corresponds to Wunderlich’s fever with a protracted pyrogenic phase of remittent nature, whereas the second type of “fièvre synèque” matched up Wunderlich’s intermittent fever. This conclusion is also supported by comments made by Littré to Hippocrates’ pyretology<sup>67</sup>, in which Littré clearly differentiated intermittent and remittent fevers:

“Une fièvre intermittente laisse le malade libre de tout symptôme fébrile, et, après l’intervalle de repos, revient avec des frissons qui ramènent un autre access, le quel se termine comme le premier. Sous ce chef sont comprises les intermittentes régulières, soit quotidiennes, soit terces, soit quartes. Une fièvre rémittente est supposée avoir des rémissions et des exacerbations très distinctes et évidentes”<sup>68</sup>.

Pseudo-continue fever was a category introduced in 1838 by the French physician François Clement Maillot (1804-1894) as part of a complex of endemic diseases peculiar of hot countries<sup>69</sup>. This group of diseases, also known as “marshy poisoning”, according to the pathogenetic theories of the time was due to the seepage of miasmas from decaying organic materials. The role of heat was to favor the production of miasmas, which were then absorbed by the body. Therefore, according to Littré, climate heavily influenced the type of fever displayed in the course of the illness. If the air was dry and humid, the fever became continuous. On the other hand, if the air was muggy and humid, the fever became remittent because the atmosphere was full of fumes from the ground. In other words, intermittent, remittent, and pseudo-continue fevers were three different degrees of the same miasmatic intoxication, whose appearance changed depending on the climate. It could also change during the disease in the same patient. At the beginning it could be continuous because air was parched and burning but, if temperature became more moderate and the air purified, fever might become intermittent or remittent. For this reason, fevers of hot countries differed from those of temperate climate, the radical difference being the possibility of fevers of hot countries to change into each other. In fact, according to Littré, “the domination of remittent fevers follows a decreasing progression from the equator to the cold countries”<sup>70</sup>. For the same reason French and English physicians practicing in the African colonies were the most experienced doctors in the treatment of these fevers. So, regarding Alexander’s

<sup>65</sup> WUNDERLICH 1871, 246.

<sup>66</sup> WUNDERLICH 1871, 244-245.

<sup>67</sup> LITTRÉ 1840, 538-582.

<sup>68</sup> LITTRÉ 1840, 577-578.

<sup>69</sup> MAILLOT 1838.

<sup>70</sup> LITTRÉ 1840, 582.



death, Littré concluded that la cause efficiente de la fièvre est placée tout entière dans l'influence climatologique. En effect, le climat chaud de Babylone suffisait pour donner à Alexandre une fièvre continue et rémittente, genre de maladie naturel à de semblables contrées<sup>71</sup>.

In 1856 George Grote (1794-1871) in his most famous *History of Greece* cited “some remarks from Littré attached to Didot’s *Fragm. Script. Alex. Magn.* p. 124”<sup>72</sup>. Grote alluded to an 1846 edition of Arrian’s *Anabasis* by the types of Firmin Didot<sup>73</sup>. This work, better known as *Fragmenta Scriptorum de Rebus Alexandri M.*, was a collection of fragments of the lost historians of Alexander published by German philologist Karl Müller (1813-1894) as a volume of his larger *Fragmenta Historicum Graecorum (FHG)*. Littré’s comments quoted by Grote were nothing more than the reprint of portions of the text of 1844, precisely the entire first page and part of the third page discussing Alexander’s fever.

Taken together, these evidences clearly demonstrate that, in his first work on Alexander’s death published in 1844, Littré attributed Alexander’s death to a pseudo-continue fever, whose description is reminiscent of that of typhoid fever, if anything.

### Littré’s second work of 1853

In 1853 Littré published his second and last article on Alexander’s death. In this work Littré analyzed the death of some historical characters (Alexander the Great, Germanicus and Britannicus), for whom poisoning was traditionally suspected. The article was entitled *De la science des poisons considérée dans l’histoire*<sup>74</sup>. It was, therefore, a toxicological work, according to Littré’s definition of toxicology : “On donne le nom de toxicologie à l’ensemble des connaissances qui ont pour objet les poisons”<sup>75</sup>. Littré’s renewed interest in the possible poisoning of historical characters stemmed from the fact that, in the meantime, modern knowledge in the toxicological field had greatly expanded, especially as regards the possibility of diagnosing poisoning by post mortem examination of human specimens. Fundamental to this aim had been the publication of a *Traité des poisons* by the Spanish physician Mathieu Bonaventura Orfila (1787-1853)<sup>76</sup>, the founder of forensic toxicology, Littré wanted to assert that, if modern techniques for detecting poisons had been available at the time of Alexander, no one would have even thought about poisoning.

This work was much longer than that of 1844. The first nine pages were devoted to discuss Orfila’s work and his merits in the field of toxicology. Then, Littré introduced

<sup>71</sup> LITTRÉ 1844, 433.

<sup>72</sup> GROTE 1856, 256-257 n. 2.

<sup>73</sup> MULLER 1846. The book is divided in several parts, each one with its own page numbering. Littré’s comments are in the section *Scriptores Rerum Alexandri Magni*, under the title *Eumenes Cardianus et Diodotus Erythraeus* (123-124).

<sup>74</sup> LITTRÉ 1853.

<sup>75</sup> LITTRÉ 1853, 666.

<sup>76</sup> Orfila was the protagonist of the “Lafarge murder case”, a notorious murder trial held in France in 1840. It was Orfila that found definite traces of arsenic in the body of Marie Lafarge’s husband. Based on this evidence, Madame Lafarge was found guilty of murder. The medical literature around the mid-19<sup>th</sup> century is full of cases like this. A sensational process in 1862 was that of dr. Couty de la Pommerais, who poisoned two wives with digitalis. The doctor was framed by a series of experiments conducted by forensic doctors Tardieu and Roussin, who administered extracts obtained from the organs of his deceased wife to dogs, rabbits and frogs. All animals died with symptoms of digitalis poisoning (the paper “Scientifica miscellanea” *Quarterly Journal of practical medicine and surgery*, 35 (1864): 245-255, by an unknown author). Found guilty, de la Pommerais was guillotined in 1864.

Alexander's case as the first example of how modern medical knowledge could help clarify ancient mysterious cases. Littré began summarizing the arguments in favor of the poisoning hypothesis:

“Des bruits d’empoisonnement courunt, on le sait, après la mort d’Alexandre...Au moment de la catastrophe [Alexander’s death], un homme sur tout se trouvait dans une situation menacée et par conséquent menaçante: c’était Antipater...On prétendait, que ses services avaient attiré sur lui, non la faveur, mais la haine et le soupçon [of Alexander]; de plus, la mère du roi qui était en querelles continuelles avec Antipater, ne cessai d’exciter l’esprit de son fils contre ce général. Aussi est-ce lui que la rumeur accusa de la mort d’Alexandre”<sup>77</sup>.

At this point Littré started demolishing the poisoning hypothesis. First, he gave details of the clinical course of last illness of Alexander, as reported daily by “Éphémérides royales”. Being a philologist, Littré clarified that he based on the tradition of Arrian and of Plutarch because their versions were concordant with each other: “Sa dernière maladie y a figuré, et des extraits concordans ont été conservés par Arrien et par Plutarque... Voilà le récit authentique”. Once this description was finished, Littré rhetorically asked if “est-il possible de l’interpréter médicalement?” He had no doubts about it:

“D’abord remarquons que, dans tout le cours de ce récit, il n’est question que de l’état fébrile du roi, et qu’on mention neaucun autre symptome que de la fièvre. On ne parle ni de douleur en un point du corps, ni de gêne de la respiration, ni de toux, ni de rien, en un mot, qui puisse indiquer une inflammation locale. C’est donc une fièvre qu’eut Alexandre”<sup>78</sup>.

After asking if “il y a dans la description que nous venons de cite assez de traits conservés pour qu’on puisse diagnostiquer, même rétrospectivement, quelle fut la maladie qui emporta le roi”, Littré positively answered stating:

“Ce qui est caractéristique, ce sont les apyrexies du commencement. Une fièvre qui dure onze jours, qui offre à son début des intermissions et qui finit per devenir continue... ces fièvres sont communes dans les pays chauds, et que plusieurs médecins de l’Algerie ont designées sous le nom de pseudo-continues”<sup>79</sup>.

Therefore, as in the previous work of 1844, Littré repeated that Alexander had died of a pseudo-continue fever. This time, however, Littré more precisely identified the intervals of the early stages as the main characteristic of Alexander’s fever, lasting eleven days, progressively worsening and finally becoming continuous.

In 1855 Littré published his famous *Dictionnaire de Médecine* in which he precisely clarified what he meant for “pseudo-continue fever”: “On donne ce nom à des fièvres remittentes, qui prennent le caractère continu”<sup>80</sup>. He also gave definitions of intermittent and remittent fevers that could be used today for teaching purposes:

“Les fièvres intermittentes sont celles qui apparait et disparaît successivement, à des intervalles plus ou moins éloignés, intervalles pendant lesquelles il n’exist

<sup>77</sup> LITTRÉ 1853, 673-674.

<sup>78</sup> LITTRÉ 1853, 677-678.

<sup>79</sup> LITTRÉ 1853, 677-678.

<sup>80</sup> LITTRÉ 1853 533.

aucune trace de mouvement fébrile. Tout accès de fièvre intermittentes se partage in trois temps ou stads distincts: le premier est marqué par un refroidissement général, avec tremblement; le second, par le chaleur; le troisième, par le suer. Au troisième stade succède apyrexie”<sup>81</sup>; “On donne l’épithète de *remittentes* aux fièvres qui, sans cesser d’être continues, ont des redoublements au commencement et des simples paroxysmes de chaleur vers la fin”<sup>82</sup>.

According to these definitions, therefore, in his opinion Alexander’s fever was quite different from intermittent fevers.

Littré had not been the first French physician to note the progressively increasing character of Alexander’s fever. In 1798 Jean François Jacques Roussille de Chamseru (1749-1822) first pointed out the specificity of Alexander’s fever characterized by paroxysms becoming progressively longer and closer until fever became continuous.<sup>83</sup> Roussille-Chamseru used the expression of “marche de la pyrexie” to describe this trend of Alexander’s fever. He also described this feverish course was as an “ascension lente à oscillations ascendantes”, markedly different from the “marche suraiguë” typical of intermittent malarial fevers<sup>84</sup>. Roussille-Chamseru’s observation were subsequently reiterated by Henri Fouquet (1727-1808), professor of *clinique médicale* at the Faculty of Medicine of Montpellier, who defined Alexander’s fever as “sous-continue”<sup>85</sup>.

As in the 1844 work, Littré repeated that Alexander’s fever was typical of hot countries. In search of the possible occasion of contagion, Littré suggested that Alexander had been exposed to miasmas when “il venait de faire avec quelques vaisseaux une promenade dans les marais que forme l’Euphrateau-dessous de Babylone, et c’était là un ennemi dangereux contre le quel ne pouvaient rien son invincible phalange et ses victoires”<sup>86</sup>. In this passage Littré referred to a reconnaissance made by Alexander along the Pallacopa canal in anticipation of a possible invasion of the Arabian Peninsula. In fact, river deltas were the most dangerous type of wetland because “where the fresh water that stagnates, comes to mix that of the sea, then the danger of the effluvium is greater, because the mixture which took place by extinguishing the plants that can have life in the two separate waters, generates their further decomposition”<sup>87</sup>.

Summarizing, in the 1853 article Littré asserted again that Alexander had died of a pseudo-continue fever caused by effluvia of marsh origin, to which the king had been exposed during his journey along the Pallacopa. The disease was characterized by a single symptom, a fever of remittent nature at the beginning becoming progressively continuous, without any additional organ symptomatology<sup>88</sup>. This conclusion did not differ at all from that reached in the text of 1844. However, in the 1853 text Littré additionally discussed the therapy: “un bon médecin anglais ou français habitué à traiter les maladies des pays chauds” would have been able to cure Alexander using “au début

<sup>81</sup> LITTRÉ 1855, 531.

<sup>82</sup> LITTRÉ 1855, 1071.

<sup>83</sup> ROUSSILLE-CHAMSERU 1798.

<sup>84</sup> DECHAMBRE 1878, 249-250.

<sup>85</sup> FOUQUET 1804, 290-300.

<sup>86</sup> LITTRÉ 1853, 677-678.

<sup>87</sup> ROSANELLI 1870, 114: “Ove all’aqua dolce che stagna, venga accidentalmente a mescolarsi quella del mare, allora il pericolo dell’effluvio è maggiore, chè la miscela avvenuta estinguendo i vegetali che possono aver vita nelle due aque separate, ingenera la loro ulteriore decomposizione”.

<sup>88</sup> LITTRÉ 1853, 677, see also DAMIANI-ELICE-PECA CONTI 2021, Table 2.

les émissions sanguines [that is, bloodletting]; puis il aurait eu recours aux évacuants et au sulfate de quinine”<sup>89</sup>. This was exactly the therapy of remittent fever<sup>90</sup>.

The mention by Littré to the use of quinine sulphate may have misled many of those who identify him as the father of the “malaria hypothesis”. In fact, today it is well known that quinine and its derivatives are drugs specifically used to cure malaria. In 1853, however, before the introduction in 1899 by the Bayer company of acetylsalicylic acid under the name of *Aspirin*, quinine sulphate was the drug used in any type of fever for its antipyretic properties<sup>91</sup>, employed in the therapy of typhoid fever<sup>92</sup>, acute lobar pneumonia<sup>93</sup>, tuberculosis<sup>94</sup>, as well as of many other infectious and non-infectious diseases<sup>95</sup>. Quinine sulphate was still used in the treatment of typhoid fever for its anti-pyretic properties in 1904 at the dose of 1 g/die<sup>96</sup>. Quinine derivatives having identical anti-pyretic properties remained the febrifugal drug of choice in typhoid fever until 1950<sup>97</sup>, when introduction of chloramphenicol made them useless. Therefore, Littré’s allusion to using quinine sulphate to treat Alexander’s fever has nothing to do with malaria.

### Littré’s works of 1865 and 1872

After the two works of 1844 and 1853 Littré did not write any more on Alexander’s death. In fact, all subsequent published works were reprints of the 1853 article. The 1865 article was printed in a small collection called “Bibliothèque originale”<sup>98</sup>. This reprint corresponded to pages 673-680 of the 1853 article. Not a single word of the text was changed compared to the original. The most important feature of the 1865 edition was the presence of an “avis de l’éditeur” (René Pincebourde), who made known to the reader that the text was a “fragment critique” of Littré in which the author “prouve, contre les dires de la légende et les doutes de l’histoire, qu’Alexandre est mort, comme un mortel vulgaire, d’une fièvre mal soignée. Cette existence héroïque a eu une fine banale”. Furthermore, Littré added his own “Avertissement”, clarifying that the article was an extract from a previous work published in 1853 in the *Revue des Deux Mondes*. Summarizing his major conclusions Littré wrote:

“La croyance à l’empoisonnement d’Alexandre le Grand ne résistent pas à l’interprétation médicale des fragments concordants des Ephémérides royales, conservés par Arrien et par Plutarque. En ce qui concerne la maladie d’Alexandre, elle semblerait une période de onze jours, durant la quelle elles nous font assister aux phases d’une fièvre pseudo-continue, contractée dans le marais de l’Euphrate”<sup>99</sup>.

<sup>89</sup> LITTRÉ 1853, 679.

<sup>90</sup> MACAULAY 1831, 259.

<sup>91</sup> LOOMIS 1884, 643: “the anti-pyretic power of sulphate of quinine is established beyond question”.

<sup>92</sup> LOOMIS 1884, 643.

<sup>93</sup> LOOMIS 1884, 99.

<sup>94</sup> LOOMIS 1884, 199: “of all the anti-pyretics in the treatment of the fever of phthisis the sulphate of quinine is the most reliable”.

<sup>95</sup> BRYANT 1894, 385-572.

<sup>96</sup> SALTERINI 1904, 185.

<sup>97</sup> BUFANO 1949, 98.

<sup>98</sup> LITTRÉ 1865, 5-31.

<sup>99</sup> LITTRÉ 1865, 5-9.

As far as the work published in 1872 and erroneously quoted by Engels as the earliest, it was the plain reprint of the entire 1853 article<sup>100</sup>. It is strange that this aspect has escaped the attention of many authors writing on Littré, because it means that his medical knowledge must be dated back to 1853.

Therefore, the overall conclusion is that, during his lifetime, Littré never changed his ideas concerning the death of Alexander. For him the young Macedonian king had died of a pseudo-continuous fever of miasmatic origin typical of hot countries, whose only symptom was a fever lasting eleven days, of remittent nature at the beginning and progressively worsening to become continuous just before death<sup>101</sup>.

### The *Æsculape* article of 1927

In 1927 the last reprint appeared in the French medical journal *Æsculape* with the title of “La mort d’Alexandre le Grand”<sup>102</sup>. It was a shortened version of the 1865 reprint. Most importantly, the text was preceded by an unsigned, short preface summarizing the major achievements of Littré’s life and works, his studies in medicine without graduating, his edition of the *Œuvres d’Hippocrate* and his *Dictionnaire de Médecine et de Chirurgie*. Littré’s production on Alexander’s death was defined an essential passage of a work at the same time “historique, philosophique et critique”. The preamble concluded in this way: “Littré y prouve, contre les dires de la légende et les doutes de l’histoire, qu’Alexandre est mort, comme un vulgaire mortel, d’une affection banale et terre à terre, le paludisme”. This passage was literally taken from the “Avis de l’éditeur” of the 1865 edition. However, Pincebourde had written that Alexander had died of a “fièvre mal soignée”. Whoever wrote the preface to the 1927 article simply substituted “fièvre mal soignée” with “paludisme” in spite of any anachronism. Essentially, in this way the author of the preface arbitrarily established the equation between the term “paludisme”, introduced in medicine after Laveran’s discovery to accurately indicate “que le sang du malade est habité par l’hématozoaire de Laveran”<sup>103</sup>, and Alexander’s disease, even though Littré had always written of a “remittent pseudo-continuous” fever with characteristics completely different from “fièvre intermittentes” typical of malaria. In this way Littré became miraculously the father of the “malaria hypothesis” more than forty years after his death.

### Conclusions

Contrary to what believed by some<sup>104</sup>, during his lifetime Littré wrote only two essays on Alexander’s death, the first in 1844 and the latter in 1853. The subsequent published articles of 1865, 1872 and 1927 were just reprints of the 1853 essay. In both pieces of writing Littré stood fast in the hypothesis that Alexander had died of a pseudo-continuous fever, i.e. of a fever lasting eleven days characterized by initial phases of remission, gradually increasing, and becoming continuous a few days before

<sup>100</sup> LITTRÉ 1872.

<sup>101</sup> CITATI 2004, 75-79; DAMIANI 2012, 40-43, Table 2; DAMIANI–ELICE–PECA CONTI 2021, 227, Table 3.

<sup>102</sup> LITTRÉ 1927.

<sup>103</sup> LE DANTEC 1901, 2.

<sup>104</sup> ENGELS 1978, 225; CHUGG 2007, 31 n. 58; LIAPPAS–LASCARATOS–FAFOUTI–CHRISTODOULOU 2003, 562; STAHULJAK 2013, 148.

Alexander's death. If anything, this description corresponded to the protracted pyrogenic phase typical of typhoid fever, but it was different from the thermography of malarial fevers. Based on the miasmatic theory of infectious diseases and on previous classification of fevers by Maillot, Littré considered this type of fevers characteristic of hot countries because of the role played by heat in the production of miasmas from decaying organic materials. Alexander's fever could have been treated with quinine sulphate because it was the choice antipyretic for any type of fever. The idea that Littré was the father of the malaria hypothesis stemmed from the invention of the anonymous author of the preface to the *Æsculape* reprint of 1927, who substituted the word "paludisme" to the expression "fièvre mal soignée" used by the editor Pincebourde in his preface to the Littré's 1865 reprint. The moral of this study is that the veracity of the information handed down should not be taken for granted and that it should always be verified in the original sources.

## BIBLIOGRAPHY

- ANTELA-BERNÁRDEZ, B.; SIERRA MARTIN, C. (2018): "Alexander and the Medicine", *Karanos* 1: 35-54.
- AQUARONE, S. (1958): *The life and works of Émile Littré*, Leiden.
- ASCENZI, A. (1999): "Malaria diseases and parasites", *Parassitologia* 41.1-3: 33-38.
- BERTOLOTTI, M. (1932): *Alessandro Magno*, Torino.
- BORZA, E. N.; REAMES-ZIMMERMAN, J., (2000): "Some new thoughts on the death of Alexander the Great", *AncW* 31: 22-30.
- BRUCE-CHWATT, L. J.; DE ZULUETA, J. (1980): *The rise and fall of malaria in Europe. A historic epidemiological study*, Oxford.
- BRAUENSTEIN, J. F. (2005): "Daremberg et les débuts de l'histoire de la médecine en France", *Revue d'histoire des sciences* 58.2: 367-387. (<https://doi.org/10.3406/rhs.2005.2253>).
- BRYANT, J. H. (1894): "One hundred cases of hyperpyrexia", in W. WHITE HALE – W. H. A JACOBSON (eds.): *Guy's Hospital Reports vol. I*, London: 385-572.
- BUFANO, M. (1949): *Trattato di Patologia speciale medica e terapia*, Milano.
- CASTIGLIONI, A. (1948): *Storia della Medicina. Vol. II*, Verona.
- CELLI, A.; MARCHIAFAVA, E. (1890a): "Sulle febbri malariche predominanti nell'estate e nell'autunno a Roma", *Archivio di Scienze mediche* 14: 177-218.
- (1890b): "Ancora sulle febbri malariche predominanti nell'estate e nell'autunno a Roma", *Archivio di Scienze mediche* 14: 449-460.
- CHUGG, A. (2007): *The quest for the tomb of Alexander the Great*, AMC Publications.
- CILLIERS, L.; RETIEF, F. P. (1999): "The death of Alexander the Great", *Acta Academica* 31: 63-76
- CIRILLO, V. J. (2000): "Fever and reform: the typhoid epidemic in the Spanish-American War", *Journal of History of Medicine and Allied Sciences* 55.4: 363-397 (<https://doi.org/10.1093/jhmas/55.4.363>).
- CITATI, P. (2004): *Alessandro Magno*, Milano.
- CONAN DOYLE, A. (1900): *The Great Boer War*, London.

- CONNOLLY, M. A.; HEIMANN, D. L. (2002): “Deadly comrades: war and infectious diseases”, *The Lancet* 360: s23-s24 ([https://doi.org/10.1016/S0140-6736\(02\)11807-1](https://doi.org/10.1016/S0140-6736(02)11807-1)).
- CROTTI, D. (2005): “La Malaria, ossia la mal’aria: brevi note di una storia sociale e popolare”, *Le Infezioni in Medicina* 4: 265- 270.
- CUNHA, B. A. (2004): “The death of Alexander the Great: malaria or typhoid fever?”, *Infectious Diseases Clinics of North America* 18.1: 53-63 ([https://doi.org/10.1016/S0891-5520\(03\)00090-4](https://doi.org/10.1016/S0891-5520(03)00090-4)).
- (2007): “Prolonged and perplexing fevers in antiquity: malaria and typhoid fever”, *Infectious Diseases Clinics of North America* 21: 857-866 (<https://doi.org/10.1016/j.idc.2007.08.010>).
- DAMIANI, E. (2012): *La piccola morte di Alessandro il Grande*, Venezia.
- DAMIANI, E.; ELICE, M.; PECA CONTI, R. (2021): “The terminal aphonia of Alexander the Great, a silent herald of an ordinary death”, *Acta Medico-Historica Adriatica* 18.2: 201-228 (<https://doi.org/10.31952/amha.18.2.1>).
- DAREMBERG, G. (1870): *Histoire des sciences médicales comprenant l’anatomie, la physiologie, la médecine, la chirurgie et les doctrines de pathologie générale*, Paris.
- (1882): “L’œuvre médicale de M. Littré”, *Revue des deux mondes* 52.3: 634-671.
- DECHAMBRE, A. (1878): *Dictionnaire encyclopédique des sciences médicales*, Paris.
- DESTAING, F. (1970): “The death of Alexander”, *Presse Medicale* 78: 2391-2393.
- ENGELS, D. (1978): “A note on Alexander’s death”, *CPh* 73: 224-228 (<https://doi.org/10.1086/366434>).
- FOUQUET, H. (1804): “Sur la fièvre qui se meut par jours pairs, et sur la nature de la maladie d’Alexandre”, *Recueil Périodique de la Société de Médecine de Paris redigé par Sedillot* 21: 290-300.
- GALLUP, J. L.; SACHS, J. D. (2001): “The Economic Burden of Malaria”, in J. G. BREMAN – A. EGAN – G. T. KEUSCH (eds), *The Intolerable Burden of Malaria: A New Look at the Numbers*, (American Journal of Tropical Medicine and Hygiene, Supplement to Volume 64.1), Northbrook: 85-96.
- GARRISON, F. H. (1929): *An introduction to the History of Medicine*, Philadelphia–London.
- GOLGI, C. (1886): “Sulla infezione malarica”, *Archivio per le Scienze mediche* X.4: 109-136.
- GROTE, G. (1856): *History of Greece*, New York.
- GOUREVITCH, D. (2004): “Charles Daremberg, His Friend Émile Littré, and Positivist Medical History”, in F. HUISMAN – J. H. WARNER (eds.): *Locating medical history. The stories and their meanings*, Baltimore: 53-73.
- GOVAERTS-REGIS, J. (1941): *Un Médecin au service de l’histoire. Augustin Cabanès*, Paris.
- HALPERIN, E. C. (2006): “What or Who Killed Alexander the Great?”, *The Pharos Summer*: 19-25.

- HEILBRON, J. (2007): “Sociologie et positivisme en France au XIX siècle: les vicissitudes de la Société de sociologie (1872-1874)”, *Revue Française de sociologie* 2.48: 307-331.
- HUISMAN, F.; WARNER, J. H. (eds) (2004): *Locating medical history. The stories and their meanings*, Baltimore.
- LE DANTEC, F. A. (1901): *Le paludisme, sa prophylaxie*, Paris.
- LEE, A. (trad.) (1831): *Celsus: On Medicine. Vol. I*, London.
- LIAPPAS, I.; LASCARATOS, J.; FAFOUTI, S.; CHRISTODOULOU, G. (2003): “Alexander the Great’s relationship with alcohol”, *Addiction* 98.5: 561-567 (<https://doi.org/10.1046/j.1360-0443.2003.00384.x>).
- LITTRE, É. (1840): *Oeuvres complètes d’Hippocrate. Vol. II*, Paris.
- (1844): “Sur la maladie d’Alexandre le Grand”, in L. DE SINNER, *Plutarque, Vie d’Alexandre*, Paris: 133-138.
- (1853): “De la science des poisons considérée dans l’histoire”, *Revue des deux mondes* 4: 665-687.
- (1839-1861): *Œuvres complètes d’Hippocrate*, Amsterdam [Reprinted 1961-1962].
- (1865): *La vérité sur la mort d’Alexandre le Grand*, Paris.
- (1872): “De la toxicologie dans l’histoire et de la mort d’Alexandre”, in E. LITTRE, *Médecine et Médecins*, Paris: 393-428.
- (1927): “La mort d’Alexandre le Grand”, *Æsculape* 17: 222-228.
- LOISON, L. (2015): “Pourquoi refuser la théorie cellulaire? Le projet d’une anatomie chimique chez Charles Robin (1821-1885)”, *Revue d’histoire des sciences* 68.1: 23-45 (<https://doi.org/10.3917/rhs.681.0023>).
- LOOMIS, A. L. (1884): *Textbook of practical medicine*, New York.
- LUZI, G. (2021): “Non dimentichiamo Angelo Celli: scienziato contro la malaria e uomo contro la povertà”, *Italian Journal of Prevention, Diagnostic and Therapeutic Medicine* 4.1: 8-13.
- MACAULAY, A. (1831): *A Dictionary of Medicine, designed for popular use*, Edinburgh.
- MAILLOT, F. C. (1838): *Traité des fièvres ou irritations cérébro-spinales intermittentes; d’après les observations recueillies en France, en Corse, et en Afrique*, Paris.
- MAJNO, G. (1975): *The Healing Hand, Man and Wound in the Ancient World*, Harvard.
- MAJNO, G.; IORIS, I (2002): *Cells, Tissues and Diseases Principles of General Pathology*, Oxford.
- MERTENS, J. E. (2024): “A History of Malaria and Conflict”, *Parasitology Research* 123:165 (<https://doi.org/10.1007/s00436-024-08167-4>).
- MOULOPOULOS, S. D. (1998): “Letter to the Editor: A Mysterious Death”, *New England Journal of Medicine* 339: 1248.
- MUELLER, J. (1851): *Manuel de Physiologie, traduit de l’allemand sur la dernière édition avec des additions par A.-J. L. Jourdan, deuxième édition revue et annotée par È. Littré*, Paris.
- MULLER, K. (1846): *Arriani Anabasis et Indica*, Paris.



- MULLER, J. (1837): *Handbuch der Physiologie des Menschen für Vorlesungen*, Coblenz.
- OLDACH, D. W.; RICHARD, R. E.; BORZA, E. N.; BENITEZ, R. M. (1998a): “A Mysterious Death”, *New England Journal of Medicine* 338: 1764-1769 (<https://doi.org/10.1056/NEJM199806113382411>).
- (1998b): “Letter to the Editor: A Mysterious Death: The Authors Reply”, *New England Journal of Medicine* 339: 1249.
- OLFIELD III, E. C.; WALLACE, M. R.; HYAMS, K. C.; YOUSIF, A. A.; LEWIS, D. E.; BOURGEOIS, A. L. (1991): “Endemic infectious diseases of the Middle East”, *Review of Infectious Diseases* 13: S199-S217.
- PACKARD, R. M. (2021): *The making of a tropical disease: A Short History of Malaria*, Baltimore.
- RADET, G. (1931): *Alexandre le Grand*, Paris.
- RETIEF, F. P.; CILLIERS, L. (2006): “The death of Alexander the Great”, *Acta Theologica* 26.2 Supplementum 7: 29-43 (<https://doi.org/10.4314/acta.v.26i2.52557>).
- ROSANELLI, C. (1870): *Manuale di Patologia generale*, Padova.
- ROUSSILLE-CHAMSERU, J. F. J. (1798): “Observations médicales, extraites d’auteurs non médecins, appliquées à la description des fièvres subintrantes, et devant faire partie d’un plus grand travail”, *Mémoires de la Société Médicale d’émulation* 1: 4-23.
- RUPKE, N. A. (1998-1999): “Reflections on the place of medical history”, *Philosophia Scientiae* S2:181-197.
- SABROSKY, C. W.; USINGER, R. L. (1944): “Nomenclature of the human malaria parasites”, *Science* 100 (2592): 190-192 (<https://doi.org/10.1126/science.100.2592.190>).
- SALLARES, R. (1991): *The ecology of the ancient Greek world*, New York.
- SALTERINI, G. (1904): *Il progresso terapeutico. Annuario Pratico Scientifico per l’anno 1904*, Milano.
- SCHLEIDEN, J. M. (1838): *Beitrage zur Phytogenesis*, Berlin.
- SCHWANN, T. (1839): *Mikroskopische Untersuchungen über die Ubereinstimmung in der Struktur und dem Wachsthum der Tiere und Pflanzen*, Berlin.
- SIMIOU, M.; CODREANU, R.; CORLATESCU, A.-D.; PAUNA, A. M.; CILIEVICI, S. E. (2023): “Camillo’s Golgi Impact on Malaria Studies”, *Cells* 12.17: 1-7 (<https://doi.org/10.3390/cells12172156>).
- STAHULJAK, Z. (2013): “History as a Medical Category: Heredity, Positivism, and the Study of the Past in the Nineteenth-Century France”, *History of the Present* 3.2: 140-159.
- THOMAS, M. (2020): “Charles Robin and Émile Littré: débats sur la cellule et la continuité du vivant dans les manuels de physiologie et les cercles intellectuels parisiens dans la deuxième partie du XIX<sup>e</sup> siècle. Littérature française et savoirs biologiques au XIX<sup>e</sup> siècle, Traduction, transmission, transposition”, in T. KLINKERT – G. SEINGER (éds.): *Littérature française et savoirs biologiques au XIX<sup>e</sup> siècle. Traduction, transmission, transposition*, Berlin–Boston: 265-280.

VIRCHOW, R. (1858): *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre*, Berlin.

— (1854): “Spezifiker und Spezifisches”, *Virchow's Archi*, 6: 3-33.

WRIGHT, J. (ed.), (1840): *The letters of Horace Walpole, earl of*, Oxford, London.

WUNDERLICH, C. A. (1859): *Geschichte der Medicin*, Stuttgart.

— (1868): *Das Verhalten der Eigenwärme in Krankheiten*, Leipzig.

— (1871): *On the Temperature in diseases: a manual of medical thermometry*, London.