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'Birth, life, and death of infectious diseases': Charles Nicolle (1866–1936) and the invention of medical ecology in France

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Abstract In teasing out the diverse origins of our "modern, ecological understanding of epidemic disease" (Mendelsohn, in: Lawrence and Weisz (eds) Greater than the parts: holism in biomedicine, 1920–1950, Oxford University Press, Oxford, 1998), historians have downplayed the importance of parasitology in the development of a natural history perspective on disease. The present article reassesses the significance of parasitology for the "invention" of medical ecology in post-war France. Focussing on the works of microbiologist Charles Nicolle (1866–1936) and on that of physician and zoologist Hervé Harant (1901–1986), I argue that French "medical ecology" was not professionally (or cognitively) insulated from some major trends in parasitology, especially in Tunis where disciplinary borders in the medical sciences collapsed. This argument supports the claim that ecological perspectives of disease developed in colonial context (Anderson in Osiris 19: 39–61, 2004) but I show that parasitologists such as Harant built on the works of medical geographers who had called attention to the dynamic and complex biological relations between health and environment in fashioning the field of medical ecology in the mid-1950s. As the network of scientists who contributed to the global emergence of "disease ecology" is widening, both medical geography and parasitology stand out as relevant sites of inquiries for a broader historical understanding of the multiple "ecological visions" in twentieth-century biomedical sciences.

Keywords Parasitology · Medical geography · Relapsing fevers · Hervé Harant · Max Sorre · Ludovic Blaizot

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1 Historiographical preliminaries on disease ecology

The "Golden Age" of bacteriology ended amidst bitter arguments between epidemiologists and bacteriologists (Amsterdamska 2004). After the public health tragedy that followed the 1918–1919 influenza pandemic, bacteriology was increasingly considered too simplistic to account for complex cases of host-parasite interactions (Mendelsohn 1998)—a situation further complicated by the discovery of "filterable viruses," which, resisting traditional methods of laboratory cultures, failed to meet to the standards of Koch's postulates (Gradmann 2014).[1] But to those in tropical medicine like Patrick Manson (1844–1922) or his student Ronald Ross (1857–1932), the linear relation between germs, hosts, and disease (the "one-germ, one-disease" equation) was always a simplification of the actual bio-pathological processes observed in parasitic life forms in the tropics (Worboys 1983).

Turn-of-the-century notions such as "life cycle", "vector", "intermediate host", and "reservoir" opened-up the possibility of clarifying the origin of our "modern, ecological understanding of epidemic disease", to use Andrew Mendelsohn's apt phrase (1998, p. 303). Although the concepts and methods of early parasitology included ecological perspectives,[2] historians of science and medicine have gradually downplayed the importance of parasitology in the development of a natural history perspective on disease outside tropical medicine, from both a methodological and an institutional point of view. In particular, John Farley and Andrew Mendelsohn have rejected the possibility for parasitology to inform the intellectual agenda of "disease ecology", a term that refers to "a specific analytic framework for understanding the interactions of microorganisms and macrobial hosts" (Anderson 2016, p. 242). Because of the "uncertain relevance" of parasitological methods "to bacterial or viral diseases", parasitology could not, Mendelsohn argues, have conquered bacteriology, which was the "paradigm" science of infectious disease at the turn of the twentieth century. As Anderson recently put it: "John Farley anticipates Mendelsohn in dismissing parasitology" (2016, 245). Indeed, according to Farley, by 1880 parasitology had been institutionally segregated from "proximate" medical concerns. As it became more and more confined within the narrowly-defined borders of "helminthology," he argues, "ideas [of life cycles and intermediary hosts] were unlikely to flow from parasitism to medicine" (Farley 1989, p. 57).[3]

In addition to the neglect of parasitology on the rise of ecological thinking in medical thought, another characteristic of the current historiography of the coming-of-age of the "ecological vision" as defined by Anderson (2004) is the ambiguous role of medical geography.[4] According to him, the influence of the former on

[1] On the development of virology, the identification of new disease agents, and the development of new detecting methods, see Méthot (2016a).

[2] Tilley (2011) focuses especially on tropical medicine and its connection with the rise of ecological thinking in medical sciences. See also Worboys (1988).

[3] In a recent article, Anderson commented further that "the study of parasites often did not appeal to those committed to identifying and tracking bacteria" (2016, p. 245).

[4] For works in English on the history of medical geography, see Barrett (2000), Boloton Valençius (2000). On the relation between medical geography and disease ecology, see Arrizabalaga (2018), this issue.

the latter is at best marginal; though he cites approvingly the work of geographer Jacques M. May (1896–1975) and admits the contribution of tropical medicine on the rise of the ecological viewpoint in medical sciences, his writings bring out conceptual differences rather than intellectual, practical, or even political continuities between the two approaches.[5]

The historiography on disease ecology is presently dominated by case-studies on former British colonies or the United States (see, however, Arrizabalaga 2018; Dias de Avila-Pires 2004). The main "heroes" in this narrative are Harvard comparative pathologist Theobald Smith (1859–1934), Swiss-born zoologist Karl F. Meyer (1884–1974)—who spent most of his career at Berkeley,—Australian immunologist and Nobel-Prize laureate Frank Macfarlane Burnet (1899–1985), French-educated soil microbiologist René J. Dubos (1901–1982) who worked at the Rockefeller Institute in New York, and Australian virologist Frank Fenner (1914–2010).[6] As a result, most French researchers and non-Western scientists in general—together with their concepts, networks, research institutions, and political agendas—have been ignored or insufficiently explored, making the emergence of other "ecological visions" in the twentieth century largely invisible. The situation is now changing thanks to the recent investigation of the birth of ideas of disease ecology in former U.S.S.R. and how they were used to exert and expand their dominion over contested borderlands (Jones and Amramina 2018).

Focusing on the works of Nobel-Prize winner Charles Nicolle (1866–1936), this paper seeks to make some steps toward reassessing the significance of both parasitology and medical geography for the development of an ecological perspective on disease in France during the first half of the past century. Nicolle's contemporaries often treated him as a "genius"[7] who "projected the extraordinary film of the development [of disease] in time and space" and more recent accounts have described him as a forerunner of the modern concept of "emerging infections".[8] In contrast, and following Anne-Marie Moulin's and Kim Pelis's scholarship, this paper *historicizes* Nicolle and places his contributions within the science of microbiology of the first three decades of the twentieth century. Building on, and adding to, Pelis's *Pasteur's Imperial Missionary* (2006), I show in particular that what became known as "medical ecology" in France was not professionally or cognitively insulated from some major trends in parasitology or medical geography. On the contrary, it was

[5] For example, Anderson writes that contrary to older medical geography, disease ecology is not "determinist" and postulates an "evolutionary time scale" and "integrative models" (2004, p. 42).

[6] On Smith, see Méthot (2012), on Burnet, see Anderson (2016), on Meyer and Dubos, see Honigsbaum (2016, 2017), and on Fenner see Anderson (2017).

[7] Most books on Nicolle are written in a hagiographic perspective (e.g., Lot 1953). But see also Huet (1995). Even recent contributions depict him as the "conqueror of typhus" (Dworkin and Tan 2012).

[8] "We had never envisaged […] the dynamical evolution of infectious diseases in the course of history. One day, he [Nicolle] projected the extraordinary film of their development in time and space… He had the singular gift of deciphering […] the secret relations between the things he was interested in… […] It is the privilege of the genius" (Leriche, cited in Lot 1953, p. 65). According to Henri Mollaret, no other book was "more prophetic" than *Destin des maladies infectieuses*. "Each year, since the half century that went by has confirmed the correctness of his [Nicolle's] grand vision of infectious diseases" (1986, p. 191).

partly thanks to, and not despite or against, the work of parasitologists and medical geographers such as May and Max Sorre (1880–1962) that the term ecology moved into the scientific discourse in post-war France.[9]

I proceed as follows. After presenting an overview of the life and work of Nicolle (Sect. 2), the paper turns to his studies on relapsing fever conducted at the Pasteur Institute in Tunis (Sect. 3). Even if the "cosmopolitan" dimension of bacteria made them look different from macro parasites that rely on vectors and that such "knowledge seemed inapplicable to bacteriology" (Anderson 2016, p. 245), I show how Nicolle's work covered both types of diseases. Following an outline of his evolutionary theory of diseases based on the concepts of virulence and inapparent infection (Sect. 4), the paper moves on to the reception of Nicolle's work in post-war France by the influential Montpellier medical parasitologist Hervé Harant (1901–1986) (Sect. 5). Contrary to the standard narrative that excludes Nicolle from the network of disease ecologists, Harant takes an almost opposite position and fashions *Destin des maladies infectieuses* [*Destiny of Infectious Diseases*] published in 1933 as the "great precursor book of medical ecology", introducing its author as the main "inventor" of the field (Harant 1966a, p. 324).[10] While Harant's account should not be accepted at face-value, I argue that his medico-naturalist perspective shows nevertheless that the construction of medical ecology in France is not the result of an epistemological shift from allegedly static medical geography to dynamic medical ecology that would be simple and whole; instead, the emergence of the latter results from a close entanglement between different fields such as microbiology, parasitology, medical geography, and the local conditions of disease.

2 Typhus and "The Nicollonisation of Tunisia"

Born on September 21st 1866 in Rouen, Charles-Jules-Henri Nicolle was the second son of Aline Louvrier (1839–1925) and Eugène Nicolle (1832–1884), a medical doctor and a naturalist who once occupied the Chair of Félix Archimède Pouchet (1800–1872) in natural history. Nicolle had two brothers, Maurice (1862–1932) and Marcel (1871–1934). All three Nicolle brothers were introduced to comparative anatomy and natural history by their father. Maurice later trained in pathological anatomy at Würzburg, Germany, and in microbiology at the Pasteur Institute in Paris.[11] Charles' younger brother Marcel, in contrast, became a successful art critic, a curator at the Museum of beaux-arts at Lille, and an assistant-curator at the Louvres Museum in Paris. After completing high school at Lycée Corneille in Rouen,

[9] On May, see Brown and Moon (2004), and Arrizabalaga (2018). On Sorre, see Simon (2016).

[10] This book is an augmented version of an earlier essay titled *Naissance, vie et mort des maladies infectieuses* [*Birth, Life, and Death of Infectious Diseases*] (1930).

[11] Maurice's career started when at the request of the Sultan of the Ottoman Empire Abdul Hamid II (1842–1918), Roux sent him to Constantinople directing the Imperial Institute of Bacteriology from 1893 to 1901. On the Imperial Bacteriological Institute of Constantinople and Maurice Nicolle, see Dedet (2000, pp. 151–154).

Charles Nicolle followed his older brother at the Medical Faculty[12] before entering the Pasteur Institute, where he learned microbiology under Ely Metchnikoff (1845–1916) and Émile Roux (1853–1933).

Receiving an MD degree in 1893 with a thesis on the agent of soft chancre, Nicolle returned to Rouen the next year as Director of the Bacteriological Laboratory, a position he occupied for eight years.[13] Nicolle’s overseeing of the production of serum therapy against diphtheria (developed by Roux) was successful, although he wasn’t entirely happy with his position in Rouen. Presenting a case of the conflicting views of physicians and bacteriologists in the late nineteenth century, he resented his colleagues who resisted the growing place of laboratory knowledge in clinical medicine.[14] More importantly, he experienced a gradual hearing loss that soon prevented him from using a stethoscope and compelled him to abandon clinical practice. Fortunately for him, a position opened at the Pasteur Institute in Tunis: as its Director, to replace Adrien Loir (1862–1941).[15]

When Nicolle arrived in Tunis in December 1902, the country was still under the French protectorate (1881–1954). The 36-year-old French bacteriologist was little impressed by the poor working conditions of his new institute, which made him feel “infra provincial”; however, he soon came to appreciate the possibility of being “his own master” (Moulin 1994, p. 355). Emulating Roux’s teaching in Paris, Nicolle set out to create a “*Cours*” in microbiology. Moreover, he oversaw the construction of the Institute based on plans he helped designed. It is within this “heaven for infectious diseases”, to use the words of American bacteriologist Hans Zinsser (1878–1940), that he made some his most important discoveries about the biology of infectious disease (cited in Giroud, unpublished, p. 138).

Nicolle was rapidly at home in his new environment, though he felt increasingly alone as his hearing impairment worsened. He called himself “the isolated [one]” (“*l’isolé*”)—but he was no lone researcher. From 1909, his work on typhus with Ernest Conseil (1879–1930) won him international acclaim and, in 1928, earned him the Nobel Prize in Physiology or Medicine. In the 1930s, while he was a professor at the esteemed Collège de France in Paris and still director of the IPT, his research group was part of global efforts in disease control and vaccine production.[16] Most of Nicolle’s research on typhus, relapsing fevers, influenza, and toxoplasmosis

[12] This career choice was not dictated by an actual interest in medical science but was foremost the result of his father’s wish. Nicolle was more inclined toward literature, philosophy, and history than natural sciences.

[13] In 1895, Nicolle married Alice Avice and had two children, Marcelle (1896–1985) and Pierre (1898–1984), who went on to have a career in medicine and medical microbiology respectively.

[14] On the conflict between clinicians and bacteriologist, see Maulitz (1979), and on the dispute that opposed Nicolle to his physician colleagues in Rouen, see Pelis (2006, pp. 25–28).

[15] The post was first offered to Maurice who had returned to Paris in 1901. Owing perhaps to his generally disappointing experience at the Imperial Bacteriological Laboratory in Turkey, he declined it and Roux convinced his younger brother to accept the post of director.

[16] When typhus broke out in South America and Eastern Europe in the early 1930s, Nicolle’s research group was part of the international team composed of researchers from the United States, Mexico, and Poland. His view was that two forms of typhus existed and sometimes cohabited, namely: “new world” typhus (murine typhus) and “old world” (or historical) typhus (exanthematic typhus).

appeared over the next three decades in the *Archives de l'Institut Pasteur de Tunis*. This journal, which he created in 1906, allowed him to put on display his own work and that of his collaborators and, as his reputation grew, to bring attention to the Pasteur Institute in Tunis (Pelis 2006, p. 45).

Nicolle's fame helped attract foreign visitors, some of whom were parasitologists. For example, he had a brief visit on the eve of World War I from Russian zoologist, medical geographer, and parasitologist Evgeny N. Pavlovsky (1884–1965), a central but long-forgotten protagonist in the history of disease ecology (Jones and Amramina 2018). It was Pavlovsky who introduced the "natural-focus" framework and the concept of "parasitocenosis" that was later taken up by Harant. Pavlovsky's "natural focus framework" conceptualizes infectious diseases within well-defined, natural geographical habitats that include vectors, pathogenic agents, and other parasites found in an infected host. The "entire parasitic population", Pavlovsky wrote, "forms what may be called a *parasitocenosis*" (Pavlovsky 1937, cited in Théodoridès 1954, p. 448). Features of epidemic diseases such as plague, their particular geographical distribution as well as the potential transmission of animal diseases to humans thus depend on types of parasitism and other ecological factors, including the host population. During the 1910s, Pavlovsky frequently went on zoological expeditions to collect and study poisonous insects and animals. It is during one such expedition that he planned a month-long visit the IPT; however, arriving in July 1914, on the eve of the Great War, he was forced to leave the next morning. Before he left, Nicolle gave him 60 specimens of *Heterometrus maurus*, the common scorpion of Africa.[17] After the war ended, the two exchanged letters for many years. In 1934, Nicolle penned a short article on the occasion of Pavlovsky's scientific jubilee, recounting the unusual circumstances of their meeting (Nicolle 1935). Their correspondence, kept at the Academy of Sciences at St-Petersburg, reveals that in the ensuing decades. Nicolle continued to send Pavlovsky various goods such as insect pins, but also laboratory materials and experimental animals difficult to obtain in Russia. They also routinely exchanged their recent publications, particularly those related to parasitology, and shared their personal ambitions.

In 1923, Nicolle met with the French physician and literary writer Georges Duhamel (1884–1966), with whom he frequently visited ancient sites of civilisations in Greece and North Africa (Yoeli 1967).[18] Duhamel paid Nicolle several visits; he also promoted his literary career in the *Mercure de France* and championed the concept of inapparent infection in France,[19] which stood at the centre of Nicolle's perspective on infectious diseases. Contrary to healthy carriers who could harbour germs without developing the disease, patients suffering from *inapparent*

[17] "Mon cher Collègue, je prends des dispositions pour que vous trouviez à votre arrivée à Tunis, fin juillet, un lot important de scorpions des espèces que vous désirez." Letter (087804162600060) from Nicolle to Pavlovsky, June 7th (No year but certainly in 1914).

[18] Nicolle and Duhamel exchanged over 450 letters, many of which have now been edited and published by Hueber (1996).

[19] "The more I think about it, the more I am convinced that such a discovery [inapparent infection] has the capacity to overturn not only pathology, but also, and I would say principally, psychology." Letter from Duhamel to Nicolle, October 25th 1924 (in Pelis 2006, p. 136).

infection, Nicolle argues, would go through all the normal stages of the disease process, namely: "a period of incubation, an infectious state (septicaemia and virulence), then cure, all without a single sign to warn the observer" (Nicolle and Lebailly 1919–1920, p. 5, cited in Pelis 2006, pp. 107–108).[20] Forming "a chain from one season to the next", inapparent infections are epidemiologically significant, since they would permit "the conservation of the virus and the return of epidemics" (Nicolle 1930, p. 92).

Among the scientific visitors, Nicolle regularly hosted bacteriologist Hans Zinsser from Harvard (Fig. 1). A colleague of the noted American comparative pathologist Theobald Smith, Zinsser corresponded with Nicolle on the epidemiology, biology, and phylogeny of the elusive agent of typhus disease. First coming to Tunis in 1927, Zinsser returned several times until Nicolle's death—which, he said, "was the same order of sorrow as had been the death of [his] father" (Zinsser, cited in Wolbach 1947, p. 330). Dedicating his "biography" of typhus disease to Nicolle—"with affectionate friendship" (Zinsser 1930)—he wrote the biographical memoir of Smith for the National Academy of Science (Zinsser 1936). For Zinsser, Smith and Nicolle were among the few "great living bacteriologists" (Zinsser 1940, p. 313). Though they had different personalities, Smith and Nicolle viewed disease as a biological phenomenon like any other that must be studied in biological terms.[21] If Nicolle's ideas about the biology of infectious disease might have exerted some influence on Zinsser, (Pelis 2006, p. 321), it is likely that some of Smith's biological ideas on host-parasite equilibrium reached Nicolle through his discussions with Zinsser.

The scope of Nicolle's scientific activity and his involvement in developing public health measures in Tunis to control typhus and other infections was extensive; so much so that London parasitologist Percy C. C. Garnham (1901–1994) once described it as the "Nicollonisation of Tunisia" (Garnham 1977, p. 1101). Though hardly the only disease in North Africa, Nicolle regarded typhus as "the most urgent and the most unexplored" (Nicolle 1928). Coming in waves, it descended on the Tunisian populations during winter periods, spreading to the poor areas of cities and reaching the outskirts of towns. After observing that contagious patients, once stripped of their clothes, no longer transmitted the disease, Nicolle went on to demonstrate that humans were the reservoir of typhus—and the louse its vector of transmission.[22] Studying the lines of transmission of disease agents, developing vaccines,

[20] On the history of the concept of "healthy carrier," see Mendelsohn (2001) and Gradmann (2010). For a discussion of Nicolle's concept of inapparent infection in relation to terms such as "latent infections," "symptomless infections," and "sub-pathological infections," see Meyer (1936).

[21] Whereas *Naissance, vie et mort des maladies infectieuses* attempts to conceptualize infectious diseases as "biological phenomena," which, Nicolle argued, must be studied with a "biological mind" (Nicolle 1930, pp. 28, 30), Smith tried to make students "think biologically" about disease (Smith 1931, p. 6).

[22] Testing the hypothesis that lice on patients' clothes were the vectors of the disease, Nicolle first inoculated a chimpanzee with blood from a patient suffering from typhus. Twenty-four hours later, the animal presented the typical signs and symptoms of typhus: it was febrile, had skin eruptions, and remained in a prostrate position. Drawing blood from the chimp, he injected a toque macaque that became ill 13 days later. Dropping lice on the ill-macaque, he transferred those a few days later to another group of macaques and recorded that these individuals also contracted the disease. On these experiments, see Schultz and Morens (2008).

and implementing public health measures informed by laboratory science was also an intrinsic part of Nicolle's broader "civilizing mission" (Pelis 2006, p. 39).

Nicolle's expertise soon expanded to include a range of North African parasitic diseases: these comprise his well-known research on leishmaniosis ("Kala-Azar") and on toxoplasmosis, a disease carried by small rodents similar to guinea pigs named *gondi* (Nicolle and Manceaux 1908, 1909). In times of war, Nicolle worked closely with the Swiss-born marine protistologist Edouard Chatton (1883–1947), who later differentiated prokaryotic from eukaryotic organisms (Sapp 2005). In turn, Chatton was influential in training graduate students at the Roscoff Station in Britany and as director of the Arago Laboratory in Banyuls-sur-Mer in the south of France (Soyer-Gobillard 2002). After the war, Nicolle's work of the transmission of typhus led to his introduction of the notion of inapparent infections (Nicolle and Lebailly 1919–1920): a conceptual innovation that, he claimed, opened-up a "whole new chapter in general pathology" (Nicolle 1925, p. 149).[23] The discovery of inapparent infections was part of Nicolle's studies of "ultramicrobes" that were associated with puzzling diseases such as influenza (Pelis 2006, p. 154).

Nicolle was ambitious and had a strong and defiant personality that led him to fall out with some of his colleagues.[24] Nevertheless, he maintained friendly relationships with other directors of Pasteur Institutes such as the Sergents in Algeria (see however note 24). In Casablanca and Athens, for example, he remained close to parasitologist Georges Blanc (1884–1963), who had been his student and his collaborator in Tunis, and with whom he visited archaeological sites in Crete. During a career that spanned nearly four decades, Nicolle travelled to the Middle-East and Eastern Europe as well as to North and South America. Although saddened by the fact that he never occupied the position of Director at the Pasteur Institute in Paris, which he vowed to "rescue" amidst administrative turmoil after Roux's passing away, he had a brilliant career and became known as much for his literary and philosophical writings as for his scientific achievements—not unlike his friend Zinsser. Decorated with the Osiris Prize and the Nobel Prize, he was elected in 1930 to the Chair of Experimental Medicine at the Collège de France, a prestigious position formerly held by Claude Bernard (1813–1878), Arsène d'Arsonval (1851–1940), and later

[23] Nicolle first arrived at the concept of inapparent infection during his attempts at controlling typhus with convalescent serum. With Lebailly, he noted that certain guinea-pigs infected with typhus blood do not hitherto become resistant to the pathogen but were "inapparently" infected. 16 days after infection, blood taken from these animals was used to inoculate a monkey (*Maccacus sinicus*) that, 7 days of incubation later, showed a temperature curve typical of a typhus infection (Nicolle and Lebailly 1919–1920). Based on this concept, Nicolle mounted a critique of Koch's postulates as he disparaged the claim that "the introduction of a pure culture of a microbe will reproduce, in susceptible species, a typical infection" (Nicolle 1925, p. 150).

[24] For example, a priority dispute—which was later resolved—concerning the role of lice in transmitting typhus flared between him and the bacteriologists brothers Edmond (1876–1969) and Étienne Sergent (1878–1948) in Alger (Dedet 2013); he resented microbiologist Etienne Burnet (1873–1960), his *préparateur*, whose novels were more acclaimed than his own (Pelis 2006); his profit-oriented strategy in vaccine production clashed with Roux's policy (Pelis 1997); Nicolle's professional relations with Émile Brumpt in Paris were particularly difficult (Théodoridès 1977); and, finally, his personal relation with his brother Maurice fell apart in the 1920s, though Charles would be inspired by his brother's work in immunology—even borrowing his evocative notion of "mosaic".

Fig. 1 Charles Nicolle and Hans Zinsser in Lisieux, France (1928). Institut Pasteur/Musée Pasteur

occupied by military surgeon René Leriche (1879–1955). It was there that Nicolle brought knowledge in bacteriology, epidemiology, and parasitology to bear on the nature of infection, articulating a singular historical vision of disease and pathology.

Charles Nicolle died in 1936. He was buried in Tunis.

3 Parasitology and the natural history of disease

Disciplinary boundaries between bacteriology and parasitology were strongly defined at universities in Paris, London, and Berlin at the turn of the past century; but such professional and institutional barriers were easily crossed, if not entirely collapsed, in colonial contexts, where institutions of this sort simply did not exist—and where the issue of infectious disease dictated more pragmatic approaches. The constant shift from the study of bacterial (including viral) to parasitic diseases in Tunis was also natural to Nicolle because parasitology was itself, as Moulin noted, "an extension of microbiology" under the French Pasteurian program (1996, p. 160). It was physician-zoologist and medical entomologist Raphael Blanchard himself (1857–1919) who portrayed parasitology "as something that followed naturally from bacteriology" and who depicted it as the "most recent stage" in scientific medicine (Osborne 2014, p. 208). Bacteriology did not, as Mendelsohn argues, have to be "conquered" by parasitology to become more "ecological"; the ecology of host-parasite interactions was, in Blanchard's view, its natural development.[25] Insights into the Tunisian context and its parasitic diseases, together with knowledge and expertise in medical parasitology he assembled, gave Nicolle an edge in analysing the intricate host–pathogen relations in terms more biological than used in traditional bacteriology. Guided by the specific conditions encountered in Tunis and the

[25] For Koch, too, parasitology was a natural extension of bacteriology, although he never became much of an ecologist. See Gradmann (2010).

specificity of the intellectual disciplinary context, he turned his microscope to bacterial, viral, and protozoal diseases—the "permanent companions of our existence" (Nicolle 1930, p. 6)—and studied those in veterinary as well as in human medicine. Nicolle's work on toxoplasmosis, for instance, revealed the existence of a parasite common to both animals and humans. Pragmatically, as Pelis noted, Nicolle "took full advantage of the fields of expertise his new collaborators brought with them" (2006, p. 71).

Coined by Blanchard, the term "parasitology" was increasingly used in biological science prior to World War I (Osborne 2017, p. 206).[26] Though impressed by Pasteur's success in controlling, preventing, and curing infectious diseases, Blanchard argued that controlling parasites was key to pressing problems in colonial medicine (Blanchard 1902, cited in Osborne 2017, p. 423).[27] Certainly, Blanchard's claim that parasitological knowledge was critical to achieving the political goals of the French government in North Africa resonated with Nicolle's view of the role of colonial medicine and his own appreciation of the situation in Tunis. In shining the light of Pastorian science on the pathological conditions in Tunisia, Nicolle sought not only to improve the local environment in ways that would contain extant parasitic diseases and resist "new" emerging threats, but also to expand the frontiers of Western civilisation (Pelis 2006). Contrary to Madagascar, the French colony to which Blanchard's comments were directed, the source of diseases responsible for thousands of deaths annually in Tunis was not "always and uniquely" in "an insect bite" (Blanchard 1902, cited in Osborne 2017, p. 423) but very often so, as Nicolle discovered. Nicolle's study of parasitic diseases especially focused on relapsing fevers: an ancient disease caused by a spirochete (*Borrelia*) and known for its capacity to recur. Before the Great War, Nicolle conducted his work on relapsing fevers in collaboration with two young parasitologists trained in Blanchard's laboratory in Paris: Ludovic Blaizot (1882–1954) and Georges Blanc. Their expertise in medical parasitology oriented Nicolle and his collaborators toward the development and mode of infection of the spirochetes, which in turn helped account for their intriguing "disappearance" in the blood of individuals recovering from relapsing fever.

With a background in zoology, medical parasitology, and the new technology of dark-field microscopy, Blaizot was sent to Tunis in 1910 by Blanchard and his assistant Émile Brumpt (1877–1951)—the author of a widely-read textbook on parasitology (6 editions between 1910 and 1949)—to study spirochetes in fowls (Fig. 2). The work of the young man was effective and Nicolle appointed him as *chef de laboratoire* a year later. Blaizot was asked to investigate a recent outbreak of relapsing fever outside Tunis suspected to be louse-borne and caused by spirochete pathogens. The Sergent brothers in Alger had called attention to the connection between lice and relapsing fever in 1908, but Nicolle doubted their claim (see Dedet 2013,

[26] On Blanchard and the history of French parasitology, see Osborne (2008), Harant (1968).

[27] Anthropologist Arthur Bordier (1841–1910), for instance, claimed that colonization could "only be accomplished through *science*" (Bordier 1884, p. xiii, cited in Osborne 2000, p. 47; emphasis in original). Pointing to the benefits in terms of health garnered for colonized populations provided a rationale for political actions. On the support of colonialism by medicine, see Pelis (2006) and Anderson (2006). For an overview of French science in colonial context, see Osborne (2005).

p. 233–234). Drawing on evidence based on human experimentation—obtained in a disturbing way[28]—Nicolle was firmly convinced that louse bites by themselves *do not* transmit the disease. But how was the disease transmitted to humans, then, if not by the louse bites? Assisted by Blaizot's ability of using an ultra-microscope and the expertise on lice in transmitting typhus, Nicolle was well—and perhaps even better—prepared than his competitors to clarify the nature of relapsing fevers.[29] It was known that spirochetes seem to disappear from human blood before reappearing in a new recurrence (or relapse) of the disease. Building on the work of British military physician and pathologist William Boog Leishman (1865–1926), who discovered that spirochetes appeared to dissolve into tiny "granules" in one of their developmental stages, Nicolle and Blaizot set out to clarify further the natural history path of infection. Using dark field microscopy, they first established that the disappearance of spirochetes in patients' blood "was only apparent" (Nicolle et al. 1912b, p. 482, cited in Pelis, p. 84; see also Nicolle et al. 1912a). They further noted that, upon returning to a visible state about a week after the infection, spirochetes ingested by lice (along with human blood) found themselves *embouteillés* (bottled up) in the arthropod. When returning to their visible stage, spirochetes—then in an acute virulent form—were in a biological dead-end, as they aggregated in parts of lice bodies (e.g. legs, antenna, thorax) from which further transmission is impracticable—unless the host is *un*bottled, that is. To liberate the parasites into the blood stream of their human host where they could fulfil their natural cycle, Nicolle and Blaizot concluded, it is necessary to kill the louse to release the pathogens inside it, a fact whose biological significance captivated Nicolle and prompted him to reflect on the "illogical" ways Nature works.[30] "The louse must be mortally wounded", Nicolle and Blaizot explained, "so that its lacunary liquid, the only thing virulent in it […] comes into contact with a scratch in the skin" (cited in Pelis 2006, p. 83). This scenario, Nicolle wrote some years later in *La Nature: Conception et morale biologiques [A Biological Perspective*

[28] Nicolle's long-term assistant in Tunis, Habib ben Abdesselem, was bitten 6515 times by the lice without developing relapsing fever. Such "extreme experimentation," as Pelis calls it, led Nicolle to "prove" a negative claim, namely: that louse bites do not transmit disease per se (Pelis 2006, p. 82).

[29] Relapsing fever is now known to be caused by various spirochete species of the *Borrelia* genus. The epidemic form of the disease is transmitted by lice while the endemic form is transmitted by ticks (Meri et al. 2006).

[30] "Les microbes qui causent la fièvre récurrente mondiale, les spirochètes, absorbés avec le sang du malade par le pou, seul agent de transmission de l'infection, subissent, dans l'organisme de l'insecte, un cycle de transformations. Ce cycle consiste dans la division des spirochètes en granules. Il aboutit à la production, à partir de ces granules, de nouveaux spirochètes très virulents. Leur siège exclusif est le sang du pou. Les spirochètes se trouvent donc embouteillés chez l'insecte. Normalement, ils n'en sortiront pas; logiquement, la raison les condamne à n'en pas sortir. L'évolution naturelle aurait donc pour conséquence la disparition du spirochète, égaré dans la circulation du pou comme dans un cul-de-sac; et, le retour à l'homme ne pouvant se faire que par l'intermédiaire du pou, non seulement l'existence de la lignée serait compromise, mais celle de l'espèce se trouverait condamnée. […] La succession des faits qui assurent la conservation de ces spirochètes dans la nature est une chaine d'accidents qui peuvent évidemment ne pas se produire, mais qui se produisent fatalement sur quelques poux, tout au moins. Il n'en faut pas davantage pour qu'une espèce microbienne et la maladie grave qu'elle détermine se conservent. De tels faits paraissent absurdes à notre logique. C'est notre logique qui est absurde, puisqu'ils sont" (Nicolle 1934, pp. 18–20.

on the Concept and Moral Aspect of Nature], though it happens only accidentally, can be relatively common: for instance, when individuals scratch themselves when bitten by lice. In scratching the skin, fingernails facilitate the entrance of the parasite in the lesion and the blood stream (Nicolle et al. 1914–1916, p. 25, in Pelis 2006, p. 83). With Blanc, also from Blanchard's parasitology laboratory, Nicolle considered changes in virulence in spirochetes showing that in lice, spirochetes are at the height of their virulent power when in their microscopically-invisible stage (Nicolle and Blanc 1914). A few years later, Nicolle and Lebailly determined that spirochetes are typically located near the legs and the antenna of the lice, that is, parts which are easily breakable when scratching a bite, thereby providing additional evidence for the complex louse-human route of infection they suggested (Nicolle and Lebailly 1919). Overall, Nicolle's research with Blaizot, Blanc, and Lebailly, the co-discoverer of inapparent infection, set him on the path of disease evolution: a perspective that, when at the Collège de France in Paris in the 1930s, he developed further still, building on the role of inapparent infection and the notion of mutation.

4 Variable virulence and the evolution of disease

Since Pasteur's work on chicken cholera and anthrax, evidence of physiological adaptations of microorganisms to host tissues accumulated, thanks to a number of studies of changes in virulence. Pasteurian microbiology as a whole, indeed, turned on the concept of variable virulence (Mendelsohn 2002).[31] In the course of his studies, Pasteur observed that virulence is not a fixed property of a microbe, but is relative to the host. Virulence, he noted, is "essentially modifiable"; it is a property that can be augmented and lowered by serially transmitting a microbial strain in different laboratory animals such as dogs, guinea pigs, rabbits, or sheep (Pasteur 1883, cited in Latour 1988, p. 64). Pasteur and his collaborators work on variable virulence goes to the heart of vaccine production because it is crucial to exert control over such biological variations to ensure the manufacture of consistent and standardized vaccines and other therapeutics agents (Mendelsohn 2016). In addition to explaining the changing behaviour of infectious disease during epidemics, Pasteur speculated that variable virulence could account for the natural appearance of new diseases such as smallpox, syphilis, yellow fever, and typhus (see Moulin 1992). He was not alone in thinking about the origins of new diseases at the time: in his *Étude sur les maladies nouvelles et les maladies éteintes [A Study on New and Excinct Diseases]* (1869), the French physician Charles Anglada (1809–1878) documented the "ebbs and flows in the prevalence of disease" (Dubos 1959, p. 415). Pasteur's research on variable virulence and vaccines, Mendelsohn argues, was perhaps "the earliest place of sustained experimental cellular-level in vitro research on phenomena understood as biological variation and evolutionary mechanism" (Mendelsohn 2002, p. 28).

[31] On Pasteur's concept of variable virulence, see Moulin (1992), Geison (1995), Gayon (1995), Pelis (2006).

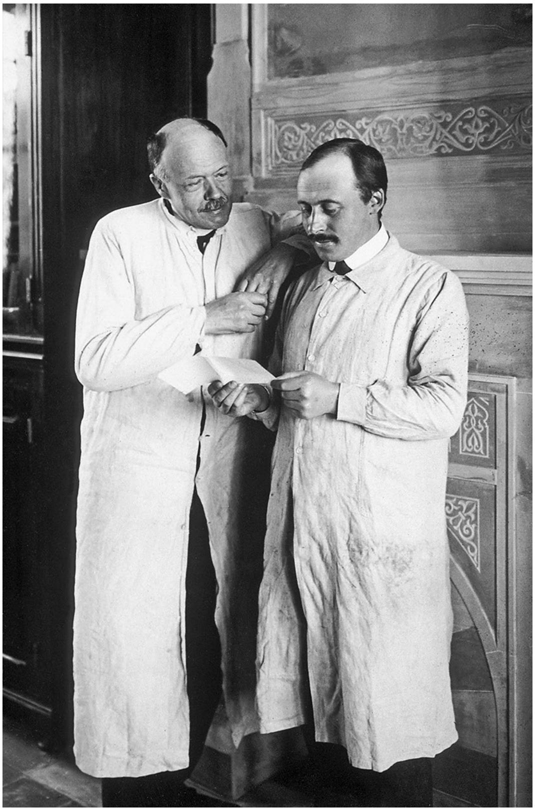

Fig. 2 Charles Nicolle and Ludovic Blaizot at the Institut Pasteur in Tunis (1920). Institut Pasteur/Musée Pasteur

This evolutionary dimension was never fully articulated by Pasteur or his collaborators themselves, and it is still a matter of debate as to whether "microbial transformism" in Pasteur's laboratory actually considered biological change *beyond* the species or only intrinsic changes within microbial species (Geison 1972; Pelis 2006). In contrast, Nicolle explored the evolutionary dimension of microorganisms much further. From Pasteur's research on anthrax and his training with Roux, he knew that virulence levels exhibited by bacterial strains could be lowered after being exposed to oxygen and restored and even augmented following the passage of strains into laboratory animals. These methods of animal transfer led him to suggest that "new" diseases could be created in the laboratory. For instance, a disease could be artificially extended to a species that did not previously suffer from it; a saprophytic microorganism could be transformed into a symptomatic disease, etc. Like Pasteur and Smith, Nicolle also assumed that controlled laboratory conditions mirror Nature's work.[32] Thus, in addition to learning from historical cases, artificially-induced pathologies were a privileged source

[32] Smith had claimed that "nature is continuously experimenting" and that "[e]xperiments are imitations of Nature with the unknown factors controlled or eliminated" (Smith 1921, pp. 1–2).

of knowledge on "naturally" occurring new diseases.[33] But whereas Nicolle's brother Maurice acknowledged Pasteur's work on the possibility of creating "new diseases" (1901, p. 153) Nicolle's own writings on the evolution of disease did not mention Pasteur's evolutionary theory of disease.[34]

The concept of virulence came to occupy a central place in Charles Nicolle's theory of diseases. Adopting Roux's definition of virulence as "the aptitude to live in higher organisms and to secrete poisons" (1939, p. 65), he went on to separate "virulence" and "toxicity", following the distinction made by his brother in his 1919 Harben Lectures on antigen and antibodies. Virulence, Nicolle writes, is the sign of "the adaptation of a microbe to an animal or vegetal species". He further assumed that virulence must be "linked to a material support" in the biology of germs (1939, p. 66). Drawing on the metaphor of a "mosaic of powers" (directly inspired from his brother's work in immunology), he resisted attributing pathogenic properties to a single chemical structure in microbes: "Although the chemical composition of pathogenic microbes or invaded tissues is useful, it can hardly enlighten us at least at present time on a variable and sensitive property known as virulence" (Nicolle 1939, p. 32). So was disease specificity reconfigured in terms of the dynamic and plastic relation between antigens and antibodies (Pelis 2006). Nicolle considered that microbes could evolve from harmless saprophytes to become virulent pathogens. Fascinated by the adaptive and potentially hereditary capacities of microorganisms such as changes in virulence, he investigates the mechanisms underpinning those processes. While some biologists of the Modern synthesis continued to claim until the mid 1940s that "bacteria have their own evolutionary rules" (Huxley 1942, pp. 131–132; see, however, O'Malley 2018), Nicolle attempted to connect variation, heredity, and evolution in microbial forms to corresponding processes in multicellular organisms. "Why", he asked "wouldn't infinitely small living beings, like higher animals, also follow the laws of transmission of hereditary characters postulated by naturalists?" (Chadli 1986, p. 9).

Long-term physiological adaptations of a parasite to its host (naturally or artificially induced) could go some way toward explaining cases of new diseases, but "in the operations of nature, not everything is characterized by slow transformation" (Nicolle 1930, p. X).[35] Was Nicolle echoing knowledge of the early days of genetics

[33] Exactly like Pasteur, Nicolle considered "history" and "laboratory" as main sources of knowledge about past diseases: "We have at our disposal two methods," he writes, "the first […] is the historical methods" and "the second is offered by the experimentation, and allows us to come to see, if not new diseases, at least new modalities of disease, giving us some justification to suppose that events took place at some earlier time in nature in the same they take place today" (Nicolle 1930, cited in Pelis 2006, p. 186).

[34] Nicolle's book on the birth, life, and death of infectious pathologies makes no reference to Pasteur's speculation about the origins of infectious diseases in history.

[35] Elsewhere, Nicolle argued that "in the creation of new diseases, in the adaptation of a virus to a living being which was until then refractory, nature uses a slow and repeated effort, whose mechanism is close to the transformations of living forms, even if it does not identify with it; sometimes, however, all of a sudden, and with no apparent preparation, nature does so by a phenomenon analogous to the mutation" (Nicolle 1934, p. 131). For him, the adaptation of microorganisms to their hosts could either be "progressive" of the result of "sudden mutations," and he saw those biological processes as analogous to the operations of the human mind in solving practical problems, namely: the slow progress of intelligence and the sudden intuition typical of scientific discovery (1934, 10).

in the United States by Thomas Hunt Morgan (1866–1945) when he identified mutation as one of the most efficient ways of producing novel pathological conditions? Kmar Ben Néfissa suggests that "it is very likely" that Nicolle "followed closely the genetic work of Morgan's 'Fly Group' without citing it in his articles" (Ben Néfissa 2006, p. 8). As Pelis observes, the American geneticist Thomas Hunt Morgan (1866–1945), who tied genes—which contain hereditary characters—to chromosomes and studied mutations under laboratory conditions, was "almost an exact contemporary of Nicolle" (2006, p. 223). A closer examination of Nicolle's ideas in the context of emerging genetics would be needed to clarify this point, however. Be that as it may, one can be confident that *Microbes and Infection* from Étienne Burnet (1873–1960), Nicolle's successor as head of IPT, with a preface by Metchnikoff emphasizing the relevance of evolutionary principles for microbiology, would have acquainted Nicolle with the genetic concept of mutation (see Burnet 1912, pp. 120, 62). And if not, British bacteriologist Fred Griffith (1879–1941), who called attention to the fact that "mutation of type among disease-producing bacteria" was "a subject of obvious importance in the study of epidemiological problems" (Griffith 1928, p. 154;) would have made Nicolle aware of the significance of these abrupt biological changes for epidemiology (Méthot 2016b).

But if a mutation could account for the emergence of virulent pathogens, it was quite unlikely that an entire group of microorganisms could lose its virulence altogether. Appealing to inapparent infections, Nicolle examined the broader immunological implications of the concept to explain the evolution of microbial diseases in history. His vast experience in colonial medicine convinced him that populations in prolonged contact with a disease generally suffer from milder symptoms than populations newly exposed to it. Crediting the joint action of technological and biological factors, he came to depict inapparent infection as the first and undetected stage of a disease and a sign of its progressive decline. In the course of their progressive attenuation, he writes, "[…] infectious diseases have passed, are passing, and will pass through inapparent forms" (Nicolle 1930, cited in Pelis 2006, p. 190). Like Smith and later Burnet, Nicolle thought that there was a "symbiotic equilibrium" that was established between the "infinitely small" and the species they infect (1934, 25).

> Every infectious disease that stricken the same species for centuries ends up losing its activity because of the increased resistance that brings about habituation among the infected species. Such habituation translates by a lowering of the illness, by the gradual diminishing of the symptoms' intensity, and by their disappearance. The last stage of the disappearance is the inapparent infection, beyond which we can take a glimpse a stage of commensalism before the definite liberation of the infected species (1934, 24-25).

Intended or not, this view echoed the "law of a declining virulence" outlined 30 years earlier by Smith (1904) and according to which the end result of an prolonged host-parasite interactions is a "stage of commensalism" (see Méthot 2012).

5 Medical ecology in the work of Parasitologist Hervé Harant

Let us return to the historiography of disease ecology. In his obituary, French parasitologist Félix Mesnil (1868–1938) considered that Nicolle's contributions could be usefully compared to Theobald Smith's perspectives on disease biology (Mesnil 1936, p. 597). Thirty years later, microbiologist Marcel Baltazard (1908–1971), a student of Brumpt and then head of the Pasteur Institute in Teheran, commemorated the centenary of Nicolle's birth with an essay in which he emphasized the role of natural history of disease in Nicolle's medical work and his major discoveries (1966). In particular, Baltazard stressed the *epidemiological* significance of Nicolle's notion of "reservoir" and highlighted his ability in combining laboratory work with the natural history approach (1966). In doing so, both Mesnil and Baltazard's essays placed Nicolle's scholarship within the boundaries of the tradition of "natural history of disease" as described by Anderson (2004). Observing that Nicolle might have exerted an influence on Burnet (viz. his use of inapparent infections in 1936), and since natural history informed Nicolle's approach to infectious disease, Pelis concurred that one might characterize his perspective as "ecological", although she was reluctant "to go so far in [her] claims as Professor H. Harant" (Pelis 2006, p. 271).

Harant's claim that Nicolle is the "inventor" of medical ecology must be subjected to historical analysis. First, what is meant by *ecological* here is unclear: how could Nicolle lay claim to have been a pioneer of ecological perspectives within medical microbiology in France or elsewhere, when he never used the term "ecology"? In fact, the term ecology existed but was not yet in widespread use in Nicolle's time; it is only in retrospect that his works could be characterized as ecological, as Harant notes: "if the word ecology had been fashionable back then" […] "Nicolle would most certainly have been using it" (Harant 1966a). Second, what did "medical ecology" mean to Harant himself? Was Harant trying to rewrite the earlier French accounts of Nicolle's career (Mésnil and Baltazard), which tied him to Smith and the English-speaking tradition? In this last section, we shall see Harant's tribute to Nicolle was shaped by his own training as a medical parasitologist on the one hand, and that what Harant meant by ecology closely parallels the older tradition in natural history and recent works in medical geography during the first half of the past century (Sorre, Braun-Blanquet, etc.) rather than the mathematical contributions to the science of ecology in Britain or in the United States (on these, see Jones 2017), on the other. In contrast to the standard narrative where proponents of disease ecology advocate some kind of Darwinian view of nature, Harant's construct of medical ecology relies especially on older German and Russian concepts such as "biocenosis" (i.e., the interdependency and dynamics of communities of living organisms) and "parasitocenosis" (i.e., the totality of parasitic species in a given host), and builds on a neo-Lamarckian view of evolutionary change (Méthot 2018; see also Loison 2011).

In the early 1920s, Harant studied zoology with marine protistologist Edouard Chatton, who was Nicolle's laboratory assistant in Tunis during World War I. It is through Chatton that "he claimed the spiritual heritage of Charles Nicolle", as Alix Delage, Harant's long-time collaborator, observed (Delage 2006, p. 207). Among

Chatton's students was future molecular biologist and Nobel Prize laureate André Lwoff (1902–1994). Inspired by the teaching of Chatton, Lwoff and Harant went on to embody respectively the molecularization of the life sciences and the natural historical methods in medical biology. Prior to that, Harant studied under zoologist Octave Duboscq (1868–1943) and was mentored by palaeontologist and fierce opponent of evolutionary theory, Louis Vialleton (1859–1929). During his education in biology at the Sorbonne, he befriended naturalist Théodore Monod (1902–2000) and met philosopher Pierre Theilhard de Chardin (1881–1955). Following his training in zoology and protistology at Banyuls-sur-Mer, Paris, and Strasbourg, Harant went on to earn Ph.D. degrees in medicine (1929) and science (1931) and a university degree in pharmacy (1937). In 1939, he passed the "aggregation exam" that enabled him to apply for the chair in medical natural history and parasitology in Montpellier. Elected to this position before the end of the Second World War, and under the patronage of Brumpt,[36] he was instrumental in the reopening and restoration of the sixteenth-century Jardin des Plantes in 1957, which contributed to the emergence of medical ecology in France. Sharpening his public health perspective, Harant worked for several years (1944–1952) for the Regional Centre for Sanitary Education, devoting himself to "epidemiology, ecology and their corollary, the prevention of disease" (Delage 2006, p. 208). For many years, Harant was a close friend of neo-Lamarckian biologist Pierre Paul Grassé (1895–1985) and a mentor for the haematologist, geneticist, and anthropologist Jacques Ruffié (1921–2004). Critical of mechanist-oriented biology, he sought to resuscitate teleological thinking in biological and medical sciences and ventured a view of the origins of species based on a "compromise between Lamarckism and mutationism" (Harant and Brygoo 1950, p. 16).

Thanks to his interest in history of science, Harant mentored the French historian of parasitology Jean Théodoridès (1926–1999).[37] His own training in parasitology made him look at host-parasite interactions as fundamental sites of disease ecologies. Borrowing the notion of "pathogenic complex" from geographer Max Sorre, he used Nicolle's framework to set Sorre's bio-geographical unit into motion and to explore its epidemiological consequences (Harant 1953). It is in this intellectual environment that Harant's biological ideas on "parasitic dead-ends" (*impasses parasitaires*) and ecological parasitocenoses matured (Harant et al. 1951; Harant 1962).

[36] "Je m'empresse de répondre à votre lettre du 23 février en vous disant toute ma joie de voir enfin la chaire d'Histoire naturelle de Montpellier sur le point d'être recréée […] En attendant le grand plaisir de savoir comment il me sera possible de vous aider, je vous adresse, mon cher Collègue, l'assurance de mes sentiments sympathiques et dévoués." Letter from Brumpt to Harant, February 26th 1945. Source: Hervé Harant Papers, BPT.B4.

[37] Trained under Brumpt in 1947, and educated in biology at Harvard (1948) and Paris (1953), Théodoridès held doctoral degrees in parasitology and humanities. He was recruited at the CNRS in 1949 and joined Grassé's laboratory in 1955. In the 1950s and 1960s Théodoridès stood at the centre of a growing, international network of medical ecology that bridge the East and the West. In addition to knowing Brumpt, Harant, and Grassé personally, he had even met Pavlovsky during one of his trips and delivered a letter on his behalf to Marcel Baltazard in Teheran in 1959, in an attempt to facilitate communication between Pastorian and Russian biomedical scientists. "M. Théodoridès vient d'arriver de Paris à Téhéran et m'a remis la carte que vous avez bien voulu lui donner pour moi." Lettre from Baltazard to Pavlovsky, Octobre 29th 1959. Source: Archives of the Pasteur Institute, Paris.

More practically, Harant studied the formation, ecology, and evolution of these bio-pathological “complexes” in the fauna and flora of the rich Montpellier area and the Southwest of France with his student Jean-Antoine Rioux (1925–2017) (Harant and Rioux 1956a, b).

Early in 1966, Harant received an invitation from Amor Chadli (1925-), head of the Pasteur Institute in Tunis, to speak at a conference on the centenary of the birth of Charles Nicolle and to contribute a paper for a special issue.[38] Responding favourably, he suggested the title “Nicolle: ‘Fondateur’ de l’Écologie Médicale”.[39] In the unpublished manuscript of his talk he marks his intention of “mingling the name of Charles Nicolle with the birth of medical ecology”.[40] The paper published in the *Archives de l’Institut Pasteur de Tunis* the same year introduces *Destin des maladies infectieuses* as the “great precursor book of Medical Ecology” and depicts Nicolle as the “greatest biologist of the first half of the twentieth century” (1966a, p. 324). Reflecting on his own work on transmissible diseases, Harant characterizes it as “fundamentally Nicollean” and observes that “[a]ll the arguments evoked by supporters of Medical Ecology are written in the works of Charles Nicolle” (Ibid.). Outlining the history of French parasitology elsewhere, Harant went on to claim that “together with Émile Brumpt […] Nicolle can be regarded as the inventor of Medical Ecology” (Harant 1968, p. 110).

Harant was not alone in mingling medical geography and microbiology at the time; Sorre himself had referred to Nicolle and Brumpt in his magnum opus *Les bases biologiques de la géographie humaine. Essai d’une écologie de l’homme* (1943). After mentioning that Brumpt’s *Précis de Parasitologie* could be cited in each paragraph, he went on to describe Nicolle’s *Destin des maladies infectieuses* as a “chef-d’oeuvre of twentieth-century French scientific literature” (Sorre 1943, p. 319). The subtitle of Sorre’s book is to some extent even more significant: *An Essay on Man’s Ecology* signposts the change from medical geography to medical ecology proposed by Sorre and enacted by Jacques May, Hervé Harant, and others a decade or so later.[41] In addition to pathogenic complexes, Harant adopted the terms “biocenosis”—coined in the nineteenth century by Karl Mobius (1825–1908) (Mobius 1883 [1877]); and “parasitocenosis”, a term usually attributed to Pavlovsky (Jones and Amramina 2018). Drawing on Pavlovsky’s “biocenological studies applied to

[38] Letter from Chadli to Harant, January 26, 1966; Letter from Chadli to Harant, June 30 1966. Source: Hervé Harant Papers, Institut Pasteur, Paris. Box ARC 22.

[39] “Je vous félicite d’organiser le centenaire de NICOLLE. Je pense pouvoir vous envoyer 5 ou 6 pages intitulées: ‘Nicolle, fondateur de l’Écologie Médicale’”. Letter from Harant to Chadli, February 7, 1966. Source: Hervé Harant Papers, Institut Pasteur, Paris, Box ARC 22.

[40] Harant, “Unpublished manuscript.” Source: H. Harant Papers, Université de Montpellier.

[41] Historians have long wondered whether the writings of Sorre had influenced Jacques May’s work on medical geography, and in particular whether the former “borrowed” the concept of “parasitic complexes” from the latter (Akhtar 2003). A recent article has shown that it was May who borrowed the concept from Sorre: “J’avais depuis longtemps le désir de prendre contact avec vous. J’ai lu, non seulement vos livres récents sur les *Fondements de la géographie humaine*, mais votre article original (je n’en connais point qui lui soit antérieur) paru dans les *Annales de Géographie* le 15 janvier 1933. […] C’est à vous, Monsieur, que l’on doit l’idée féconde de considérer la maladie comme un complexe pathogène.” Letter from May to Sorre, May 23rd, 1949, New York. Source: Simon (2016).

parasitological problems" (Pavlovsky 1937), Harant promoted the science of "*biocénotique*" (Harant et al. 1951; Harant and Jarry 1957) that considers both the "terrain" and the parasite, in the spirit of the Montpellier Medical School.[42] In their note on "Biocénose et prasitologie médicale", for instance, Harant proposed the term "parasitocenotic ecology" to characterize the kind of medical natural history he pursued (Harant et al. 1951, p. 150).

Harant long attempted to bring the fields of parasitology and bacteriology closer to one another. For him, the academic distinction between the two does not represent natural divisions in the world. As he emphasized in his opening discourse as Chair in Medical Natural History and Parasitology in 1945, "parasitology and bacteriology" are "neighbouring fields" (1946, p. 11). They are "sister disciplines" whose frontiers are "difficult to delineate" from a "systematic", a "bacteriological", "immunological", and "experimental" point of view (Harant 1946, pp. 9–10). As to the latter, Harant argued—in line with Nicolle's thinking—that "the application of bacteriological methods brought parasitic diseases into the experimental domain", exposing inapparent illnesses as well as animal reservoirs (Ibid., p. 10). Immunological theories, he claimed further, show that "no essential difference can be detected between the two types of aggression and the reactions through which the human organism responds to them" (Harant 1969, p. 232). Writing on laboratory diagnostics in 1956, Harant considered that bacteriology and parasitology share similar techniques, though both fields present significant theoretical differences: the parasitologist, Harant writes, "is primarily a naturalist". He described himself as a "total ecologist, versed in the biocenotic techniques, and knowledgeable about the pathogenic environment of its object". In contrast, the bacteriologist is only "at times a naturalist" and he must usually "think as a physiologist and as a physico-chemist" (Harant and Rioux 1956b, p. 402). Nevertheless, these two "temperaments" should not oppose but complement each other. Indeed, a few years later, Harant contended that to become a parasitologist in the Montpellier school, one has to be, firstly, a physician able to interpret diagnostics correctly; secondly, a biologist versed in bacteriological and immunological techniques; and thirdly, a field naturalist able to detect pathogenic complexes and study their interactions in the field. In brief, a parasitologist must "bring medical ecology to the service of dynamic epidemiology" (1967, p. 2).

This is why he thought that he greatest thing about Nicolle's scholarship is that he trained as a bacteriologist but "most often thought as an ecologist" (1966a, p. 329). Regretting the social and political hijacking of the term "ecology" in the 1950s and 1960s, Harant would have instead kept in place the old expression, "natural history" to characterize the study of biocenosis (Harant 1966c). For him, the patient observation and classification of nature's microscopic agents to unravel their epidemiological consequences and to examine their broader historic-natural significance should continue to be a priority for the life sciences and medicine in spite of, or perhaps because of, the growing molecularization and the rise of experimentalism in those

[42] The glossary of Pavlovsky's book on the "nidality" of disease lists a number of cognate terms such as "biopathocenose," "parasitocenose," "biogeocenose," and "biocenology" (Pavlovsky 1966, pp. 246–250).

disciplines. As a naturalist, the power of synthesizing and organizing a vast body of facts, of producing useful and pertinent classifications, were, for Harant, of utmost importance and should not be obscured by new, molecular-genetic approaches. Although he recommended handling the term "ecology" with care (seeing it not as "a science" but as a "means of knowing" within the broader biological sciences) (Harant and Jarry 1957, p. 402), Harant's tribute transformed Nicolle's bio-epidemiological approach into more fashionable and applicable ecologically-based concepts. Thus, if Nicolle is one of the intellectual "inventors" of medical ecology, Harant and his students, and in particular Rioux, have brought his ideas to the field and developed them further (Méthot 2018).

6 Conclusion

Trained in medicine and in Pastorian microbiology in Rouen and Paris, Nicolle became a leading and influential scientific figure who introduced a dynamic view of disease. Drawing upon history and biology, he studied the "fate of diseases" at individual, collective, and historical levels within the French colonial context in North Africa over three decades. Widening the notion of "specificity" beyond the rigidity of the one-germ one-disease paradigm, Nicolle described the plasticity of microbial virulence in terms of a mosaic of powers. Relapsing fevers, typhus, and other inapparent infections he studied in Tunis revealed the importance of reservoirs of potentially pathogenic germs that remained hidden between epidemic outbreaks, in both human and animal populations (Nicolle 1930, pp. 51–52). These concepts occupied a central place in medical bacteriology and public health, though advances in those fields based on these and similar conceptualizations were slower than expected in delivering their promises during the first three decades of the twentieth century (Gradmann 2016).

Returning to historiography, Nicolle's work seems at first sight to vindicate Mendelsohn's argument that "ecological" perspectives on disease entered medicine from the side of bacteriology, which underwent radical conceptual and methodological changes after the 1918–1919 pandemic. Yet, this conclusion should be resisted, at least partly. Indeed, as noted earlier, bacteriology did not need to be conquered by parasitological methods and concepts to become competent, or to show openness to the role of "ecological" concepts in medicine. Far from being resistant to the influence of the "premises of parasitology", Nicolle effectively combined field work with laboratory work, researching the natural history of both bacterial (even viral) and parasitological diseases (Fig. 3). Here, however, his receptivity to these different influences had less to do with his Pasteurian training in Paris than with the fact that, in the Tunisian context, parasitology and bacteriology were "neighbouring disciplines" (to use Harant's words), with no clear borders between them—in theory or in practice. Like Smith, Nicolle was able to make parasites "cosmopolitain". Local pathological conditions dictated pragmatic measures to combat diseases, and Nicolle's Pastorian interest in the production of vaccine was soon complemented by his search for reservoirs in natural

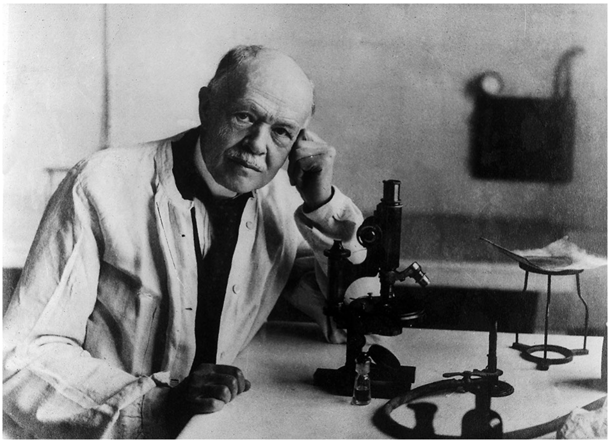

Fig. 3 Charles Nicolle in his laboratory at the Institut Pasteur in Tunis (1935). Institut Pasteur/Musée Pasteur

human or animal populations, assisted by the notion that virulent microbes can remain hidden in between epidemics, and, one day, lead to an outbreak.

One goal of this paper was to further our understanding of Nicolle's place in the network of disease ecology. I have shown how Nicolle developed personal and professional relations with several of the main pioneers of disease ecology, including Zinsser and Pavlovsky, and how the Pasteur Institute in Tunis became a place open to ecological thinking in medical sciences. But attending to Nicolle's scholarship matters for another reason: it helps make the connections between medical ecology and medical geography, at least in the French context, more visible and pertinent. Medical geographers such as Sorre did not uphold to a passive and deterministic view of health and disease; rather, they actively took part in the branding of the new field as medical or disease ecology, drawing on Nicolle and Smith to do so. Both Nicolle's historical epidemiology framework and Sorre's concept of a pathogenic complex (Sorre 1933, 1943) came together in Harant's own parasitological studies; and Harant, in several venues, hailed these contributions as ecological. His tribute to Nicolle was not a precursory tale, but was instead part of a broader call for "total natural history" in medicine (Harant 1966b, p. 24). Nicolle's concept of new disease resonates in modern readers' ears. Such resonance has increased since the 1980s, with the growing problem of "emerging infections", which they seem to anticipate. And yet, Nicolle's work first had to be *made* more ecological. Operated by Harant in the 1950s and 1960s, this change was not merely terminological or semantic, as it led to the institution of academic programmes, research institutes, and medical degrees in the field of "Medical Ecology" in France around that time. Harant's reliance on concepts of biocenosis, pathogenic complex, and parasitocenoses, similarly, invites considering anew the role of "the premises of parasitology", downplayed by Mendelsohn (1998, p. 304) and also to some extent by Farley (1989) in shaping the intellectual agenda of disease ecology throughout the twentieth century. More generally, and going beyond the historiography of disease ecology, this paper shows through several examples that early-twentieth century medicine was far-less dominate by disciplinary divides than commonly assumed, especially in non-university context.[43]

Lastly, historian Christoph Gradmann recently observed that the early history of medical bacteriology has been deeply researched compared to its later, twentieth-century developments (2016, p. 378). Following Anderson, Gradmann and others, I have tried to recuperate this less visible network of disease ecologists by focussing on the contributions of Nicolle and Harant. In attending to some of these neglected figures and in bringing out their connections and tracing their personal and institutional relations, I hope to have shed new light on these later developments, where knowledge in natural history and medicine came together, on the fringe of the modern evolutionary synthesis.

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[43] I thank Staffan Müller-Wille for insisting that I clarify this point.

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