CIRCULATION OR (RE)ENACTMENT?

performing the variable virulence/pathogenicity of helicobacter pylori•

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Introduction

This paper has two main objectives. The first is to propose and discuss a framework, inspired by the "agential realist" approach proposed by Karen Barad and by re-readings of recent contributions to the science studies of biology and biomedicine, for dealing with the variable modes of exis-

• Research for this paper was carried out as part of the project "Biographies of Objects and Narratives of Discovery in the Biomedical Sciences: The Case of Helicobacter Pylori", funded by a grant from the Foundation for Science and Technology, Ministry of Science, Technology and Higher Education (POCI/HCT/59430/2004). I am grateful to Oriana Brás, Ana Raquel Matos, Tiago Santos Pereira, Marisa Matias and Céu Figueiredo for their help at several stages in the preparation of this paper. Earlier versions of sections of this paper were presented at the joint Conference of the Society for Social Studies of Science and European Association for the Study of Science and Technology (August 2004, Paris) and at the Workshop ""The Circulation of Science and Technology: Places, Travels and Landscapes", held at Instituto de Ciências Sociais, University of Lisbon (June 2006) and benefited from the comments by participants in these two events. I am the sole responsible, of course, for any remaining errors or ommissions.

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tence and enactments, through scientific practices, of biomedical entities. The second objective is to draw on that framework to offer an exploration of the ways in which virulence and pathogenicity (and their variability) have been enacted in research on a specific pathogen, *Helicobacter pylori*.

The choice of this particular topic, and why the proposed framework is regarded as an appropriate way of approaching that topic, requires some explanation. The variability in virulence held a central place in the concerns of early bacteriologists. The concept was crucial for understanding variations in outcomes of infection not only within, but also between populations. The development of effective vaccines, which relied on the capacity to reduce or control the action of the pathogens to be inoculated, was itself dependent on variations in virulence and on the possibility of "taming" it. According to Mendelsohn,

> this almost purely operational concept [virulence] delineated the international landscape of early bacteriology on many levels, intellectual and practical, and in various, even contrary ways. This theoretically emptiest of key concepts was the hub of a theory. Upon it turned a whole structure of etiological, epidemiological, and biological explanation. Together with its counterpart concepts of the host, such as resistance and immunity, differential susceptibility and predisposition (…), variable virulence defined the field of conceivable relations between microorganisms and their hosts, whether in disease or health.[1]

[1] J. Andrew Mendelsohn, "'Like All That Lives': Biology, Medicine and Bacteria in the Age of Pasteur and Koch, *History and Philosophy of the Life Sciences*, 24 (2002): 3-36, on 17-18.

Since the times of Pasteur and Koch, it is not clear at all whether "virulence" has actually overcome its status of "theoretically emptiest of key concepts". Its relevance for etiological, epidemiological and biological explanation of infectious disease, that "complicated revolution within the complex life unit",[2] however, has persisted. The theoretical meanings attached to virulence have come to be understood in relation to its specific enactments in material/discursive procedures, constituted through biological, biomedical and epidemiological practices.

The circulation of pathogens and of the practices through which they are identified and performed as causes of disease, as well as their uses as model organisms, have been major themes in STS approaches to biomedicine and health and in studies in the history of medicine and health, especially those informed by STS.[3] Recent contributions to

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[2] Ludwik Fleck, *Genesis and Development of a Scientific Fact* (Chicago: University of Chicago Press, 1979, 1st ed. 1935), 61.

[3] See, for instance, Bruno Latour, *The Pasteurization of France* (Cambridge, Massachusetts: Harvard University Press, 1988); Mendelsohn, "Biology, Medicine and Bacteria"; Gerald L. Geison, *The Private Science of Louis Pasteur*, (Princeton: Princeton University Press, 1995); Geison, "Organization, Products, and Marketing in Pasteur's Scientific Enterprise, *History and Philosophy of the Life Sciences*, 24 (2002): 37-51; Gerald L.Geison and Manfred D. Laublicher, "The Varied Lives of Organisms: Variation in the Historiography of the Biological Sciences", *Studies in the History and Philosophy of the Biological and Biomedical Sciences*, 32 (2001): 1-29; Wolfgang U. Eckart, "The Colony as Laboratory: German Sleeping Sickness Campaigns in German East Africa and in Togo, 1900-1914", *History and Philosophy of the Life Sciences*, 24 (2002): 69-89; William F. Bynum, "The Evolution of Germs and the Evolution of Disease: Some British Debates, 1870-1900", *History and Philosophy of the Life Sciences*, 24 (2002): 53-68; Michael Worboys, *Spreading Germs: Disease Theories and Medical Practice in Britain, 1865-1900* (Cambridge: Cambridge University Press, 2000); Henrique Cukierman, , *Yes, nós temos Pasteur. Manguinhos, Oswaldo Cruz e a história da ciência no Brasil* (Rio de Janeiro: FAPERJ/Relume Dumará, 2007); Ilana Löwy, *Virus, moustiques et modernité: La fièvre*

STS and "naturalistic" philosophy of science have reinforced the notion, suggested or openly endorsed by some of these studies, that what is at stake in understanding the situated modes of existence of the phenomena biomedicine and the health sciences (and the sciences in general) engage with is how these phenomena arise through specific practices which enact material reconfigurations of the world producing new objects in a diversity of settings, something that the notion of "circulation" fails to capture in an adequate way.[4]

Biomedicine and biomedical research, indeed, offer a particularly interesting field for exploring the ways in which the production of knowledge is entangled with the world, is part of it and generates differences that matter, in the double sense of becoming matters of concern and of reconfiguring the materiality of the world.[5] Following the modes of

jaune au Brésil entre science et politique, (Paris: Éditions des Archives Contemporaines, 2001).

4 Joseph Rouse, *How Scientific Practices Matter: Reclaiming Philosophical Naturalism* (Chicago: University of Chicago Press, 2002); Joseph Rouse, "Barad's Feminist Naturalism", *Hypathia*, 19 (2004): 142-161; Werner Callebaut, *Taking the Naturalistic Turn: How Real Philosophy of Science is Done* (Chicago: University of Chicago Press, 1993).

5 Karen Barad, Meeting the Universe Halfway: Quantum Physics and the Entanglement of Matter and Meaning (Durham, North Carolina: Duke University Press, 2007). See, Annemarie Mol, The Body Multiple: Ontology in Medical Practice (Durham, North Carolina: Duke University Press, 2002) on the performativity of medical practices and on how they make differences that matter. Mol's approach converges in crucial aspects with Barad's "agential realism". For detailed accounts and discussions of the production of biological and biomedical objects and entities as material/discursive or material/semiotic practices, see, Hans-Jörg Rheinberger, Toward a History of Epistemic Things: Synthesizing Proteins in the Test Tube, (Stanford: Stanford University Press, 1997); Peter Keating and Alberto Cambrosio, Biomedical Platforms: Realigning the Normal and the Pathological in Late Twentieth-Century Medicine, (Cambridge, Massachusetts: MIT Press, 2003). I return briefly to the convergences as well as to the differences between these approaches in the concluding remarks.

existence of biomedical phenomena and the processes through which they are brought to existence and to make a difference provides a productive approach to an "ontology in movement"[6] which cannot be extricated from knowledge-producing practices and from their accountability as part of a world in ongoing processes of reconfiguration. This paper is an attempt at exploring where these insights may take us through the elucidation of the modes of existence of a bacterium – *Helicobacter pylori* – as it appears in various shapes and associated with different properties in diverse settings. The bacterium is a pathogen generating diverse effects in different places and among different human populations, which are captured by a range of research, clinical and epidemiological practices. The research reported here is part of a broader study of a range of practices and controversies which perform *Helicobacter pylori* (H.p.) as a biomedical entity and *Helicobacter pylori* infection as a phenomenon, through the mutual definition of the boundaries of health and disease, pathogens and human actors, instruments and biomedical entities.

These practices include those which enact H.p. as an epistemic object[7] – an object which, even when stabilized and mobilized in further experimental or observational practices, is (re)enacted to search for new differences[8] –, as an established biomedical fact, and as a genetically diverse

6 Lorraine Daston, "Introduction: The coming into being of scientific objects", in *Biographies of Scientific Objects*, ed. L. Daston (Chicago: University of Chicago Press, 2000), 1-14.

7 Rheinberger, Toward a History of Epistemic Things.

8 Rouse, How Scientific Practices Matter.

organism associated with variable clinical and epidemiological outcomes.

The approach taken here is based on the conception of variable virulence/pathogenicity (the two terms will be used interchangeably throughout this paper) as a *phenomenon* – an active reconfiguration of the world that confers intelligibility to a localized situation – enacted through practices constitutive of *apparatuses*, which are productive of the boundaries or "cuts" that differentiate *objects* (such as multiple strains of H.p. or virulence-associated genes) from *agencies of observation*. This approach is inspired by recent work by Joseph Rouse and Karen Barad, and by re-readings of recent contributions to the social studies of biology and biomedicine, including those by Mol; Keating and Cambrosio; and Rheinberger, among others.[9]

The first section of the paper offers a more detailed presentation of the approach, and is followed by a summary of the history of the emergence and diverse enactments of *Helicobacter pylori* as a biomedical entity. The third section provides an account of the enactment of variable virulence/pathogenicity through specific biological and biomedical practices. The final section discusses some of the implications of this work for the reconfiguration of approaches to the enactment/performance of biomedical phenomena.

9 Rouse, How Scientific Practices Matter; Barad, Meeting the Universe Halfway; Mol, The Body Multiple; Keating and Cambrosio, Biomedical Platforms; Rheinberger, Toward a History of Epistemic Things.

The approach

The approach proposed in this paper draws on the recent work of Karen Barad and Joseph Rouse.[10] According to these authors, the objective referent of knowledge-producing practices is not an independent external world, but *phenomena*. A phenomenon may be defined as a "reproducible local material arrangement or `set-up´", such as "experimental arrangements or observational configurations".[11] "Reproducible" should not be understood as being characterized by actual repetition or regularity, but rather by *repeatability*: "what matters is not the exact reproduction of the same sequence of events, but the reproduction of a signifycant pattern despite various differences among instances of the same phenomenon. To repeat an experiment, for example, is not to do the same thing exactly, but to try to produce the same pattern in different circumstances, and perhaps by somewhat different means".[12]

Barad draws on what she describes as Niels Bohr's philosophy-physics to provide working definitions of what phenomena are. According to Bohr, the term should be applied "exclusively to refer to the observations obtained

[10] My use of the work of these and other authors takes the form of what Haraway and Barad call a "diffractive" reading of a range of contributions to STS and "naturalistic" philosophy of science. Diffraction (in contrast to reflection) allows for patterns of difference to emerge through the entanglement of readings, rather than just mirroring or juxtaposing readings. I shall come back to this point in the final section of the paper. Donna J. Haraway, Modest_Witness@Second_Millenium.FemaleMan ©_Meets_OncoMouse™: Feminism and Technoscience, (New York: Routledge, 1997); Barad, Meeting the Universe Halfway (cit. n.5).

[11] Rouse, "Barad's Feminist Naturalism" (cit. n. 4), 146.

[12] Rouse, "Barad's Feminist Naturalism", 147.

under specified circumstances, including an account of the whole experimental arrangement".[13] Barad extends and reconfigures Bohr's conception in the following way:

[P]henomena are the *ontological inseparability of intra-acting agencies* (...), not the mere result of laboratory exercises engineered by human subjects but *differential patterns of mattering* ("diffraction patterns") produced through complex agential intra-actions of multiple material-discursive practices or apparatuses of bodily production.[14]

Phenomena are thus "material configurations of the world, which are frequently, but not exclusively the product of scientific research".[15]

But phenomena also appear as material configurations of the world in so far as they "constitute a practical or `constructed´ cut between a measuring apparatus and a measured `object´.[16] No inherent boundary divides and object from its surroundings, for the location of the cut depends upon the configuration of the apparatus".[17]

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13 Quoted in Barad, *Meeting the Universe Halfway* (cit. n.5), 119.

14 Quoted in Barad, *Meeting the Universe Halfway* (cit. n.5), 206 (Italics in original).The "agential realist" framework proposed by Barad starts from the premise that relations are always prior to the relata, which are the outcomes of specific "cuts" or boundaries performed through practices and the apparatuses these practices are constitutive of. Relations are thus not made of interactions between entities existing prior to the phenomenon being considered: "A phenomenon is a specific intra-action of an `object´ and the `measuring agencies´; the object and the measuring agencies emerge from, rather than precede, the intra-action that produces them". Barad, *Meeting the Universe Halfway,* 128. For a more detailed treatment of this point, see especially Chapters 3 and 4.

15 Rouse, "Barad's Feminist Naturalism" (cit. n. 4), 147.

16 Measurement should be understood here in a broad sense, encompassing different practices allowing "causes" and "effects" to be established. Different observational or experimental "dispositifs" would be included under this broad definition.

17 Rouse, "Barad's Feminist Naturalism" (cit. n. 4), 148.

Apparatuses, in turn,

> are not preexisting of fixed entities; they are themselves constituted through particular practices that are perpetually open to rearrangements, rearticulations, and other reworkings. This is part of the creativity and difficulty of doing science: getting the instrumentation to work in a particular way for a particular purpose (which is always open to the possibility of being changed during the experiment as different insights are gained).[18]

Within this framework, concepts are meaningful only by reference to specific *material/ discursive apparatuses* which are, at the same time, phenomena and productive of phenomena. Pathogens, hosts, multiple strains of bacteria or virulence-associated genes are thus defined by reference to the apparatus that constitutes them through a "cut" between object and agencies of observation. Human actors and their agency cannot be defined separately from accounts of apparatuses and of the practices that are constitutive of the latter, either.

Rather than conceiving of objects and "agencies of observation" as coming together or interacting through specific assemblages or practices, this approach requires that they be treated as being constituted through processes of "cutting", differentiating or boundary-setting, as part of phenomena and of the situated constitution of patterns of intelligibility through the operation of specific apparatuses and of the intra-actions of these.[19] Apparatuses should thus not

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[18] Barad, Meeting the Universe Halfway (cit. n.5), 203

[19] See Barad, Meeting the Universe Halfway (cit. n.5), for a fuller discussion of these points. Readers familiar with the work of Rheinberger Toward a History of Epistemic Things (cit. n. 5), and Keating and Cambrosio, Biomedical Platforms (cit. n. 5), will notice that the experimental systems of the former or the latter's biomedical platforms may be

be equated with assemblages of humans and non-humans. They may (but must not) include humans, but it is through the working of the apparatus itself that the boundaries of humans and non-humans are established.[20]

Within this framework, virulence/pathogenicity may be defined as the outcome of a set of material-discursive practices constitutive of apparatuses, producing through their intra-actions the cuts between objects and agencies of observation or experimentation, and generating phenomena such as H.p. strains, virulence-associated genes, clinical outcomes of H.p. infection or epidemiological outcomes.

An implication of this approach, which cannot be pursued in detail here but is of particular importance for the field of medicine and health, is that, as active participants in the material reconfiguring of the world, human actors are accountable for all the consequences and effects arising from their agency. The practices of biological and biomedical researchers, epidemiologists and clinicians are accountable to a world inhabited by human and non-human agencies, whose existence is always the consequence of intra-actions they are a part of. This view, associated with current discussions within feminist science studies and feminist philosophy, provides interesting extensions and reinterpretations of pragmatist contributions to the philosophy of science, as well as of some recent contributions to the social studies of medicine and health. More generally, it points towards the

redescribed as measuring apparatuses as defined by Barad. Again, a fuller discussion of this topic is beyond the scope of this paper and will be the object of a detailed treatment in forthcoming work by the author.

20 Barad, *Meeting the Universe Halfway* (cit. n.5), 171-172 and note 434.

ongoing attempts at a reconfiguration of the relationships between ethics, epistemology and ontology, again understood not as separate domains which should be brought together, but rather as the outcomes of specific operations of differentiation and boundary-creation.[21]

The analysis of the apparatuses and practices constitutive of the phenomenon of the variable virulence/pathogenicity of H.p. is based on a close reading of a series of published papers and, in particular, of their "Materials and Methods" sections, complemented by interviews with researchers and materials from ethnographic work in a research laboratory. In spite of the criticisms often addressed in the STS literature to the inadequacy of published papers as accounts of scientific practices, the use of these materials as the main sources for the analysis that follows derives from the way they provide detailed descriptions of apparatuses and of the practices that are constitutive of them. These descriptions allow the production of traces and effects, making the process of moving from "naming actions" to "naming things" traceable[22] and displaying its performative quality.[23] In the terms of the framework adopted here, this movement

[21] For discussions of these points, see Barad, *Meeting the Universe Halfway* (cit. n.5), especially Chapter 8 (pp. 353-396); and Rouse "Barad's Feminist Naturalism" (cit. n. 4), 154-156.

[22] Bruno Latour, *Pandora's Hope: Essays on the Reality of Science Studies*, (Cambridge, Massachusetts: Harvard University Press, 1999), 119-120; João Arriscado Nunes, "Do `nome das acções´ ao `nome das coisas´: crenças e produção de objectos epistémicos nas ciências da vida e na biomedicina", in *O processo da crença,* ed. Fernando Gil, Pierre Livet and João Pina Cabral (Lisbon: Gradiva, 2004), 402-412.

[23] Barad, *Meeting the Universe Halfway* (cit. n.5); Rouse "Barad's Feminist Naturalism" (cit. n. 4), 151. On the convergences and differences between this approach and actor-network theory, see the concluding remarks.

would correspond to the intra-active process whereby "actions" produce the material/semiotic boundaries differentiating "objects" and "agencies of observation".

The papers I have drawn upon were published between 1998 and 2000 and brought together as the doctoral dissertation of their main author, submitted in 2000.[24] Additional materials included other papers quoted in these publications, an interview with their main author and ethnographic materials from two studies of the laboratory where most of that work was performed, which were carried out between 1994 and 2002, with field visits over the following years.

Limitations of space do not allow a detailed account of all the practices through which the variable virulence/ pathogenicity of H.p. is enacted as a phenomenon, nor of the range of apparatuses involved. I have thus opted for a detailed rendering of one of these practices/apparatuses and a more general discussion of how the whole project which, for the purposes of this paper, is equated with the work reported

[24] Céu Figueiredo, vacA, cagA *and* iceA *Genes of* Helicobacter pylori*: Genotyping, Epidemiology and Clinical Relevance*, Doctoral Dissertation, School of Medicine, University of Oporto, 2000; Céu Figueiredo et al, "Genetic organization and heterogeneity of the *iceA* locus of *Helicobacter pylori*," *Gene*, 246 (2000): 59-68. L.J van Doorn,. et al, "Typing of *Helicobacter* pylori vacA gene and detection of cagA gene by PCR and reverse hybridisation", Journal of Clinical Microbiology, 36 (1998): 1271-1276; L.J. van Doorn et al, "Expanding allelic diversity of Helicobacter pylori vacA", Journal of Clinical Microbiology, 36 (1998): 2597-2603; L. J. van Doorn et al, Clinical relevance of the cagA, vacA and iceA status of Helicobacter pylori, Gastroenterology, 115 (1998): 58-66; L. J van Doorn et al, "Distinct variants of Helicobacter pylori cagA are associated with vacA subtypes", Journal of Clinical Microbiology, 37 (1999): 2306-2311; L. J. van Doorn, et al, "Geographic distribution of vacA allelic types of Helicobacter pylori", Gastroenterology, 116 (1999): 823-830. All quotations are from the versions included in Figueiredo, Genotyping, Epidemiology and Clinical Relevance.

in the papers I have analysed, may itself be approached as a phenomenon.

But first, let us look briefly at the making of *Helicobacter pylori* as a biomedical entity and as a pathogen.

Helicobacter pylori: a short biography

In 1982, two Australians, the pathologist Robin Warren and the physician Barry Marshall, successfully cultured bacteria from gastric biopsies. The results of their work were first published in 1984, after several unsuccessful attempts. Although bacteria had been reported to be found in the gastric region of several non-human animals and in humans since the late 19th Century, colonization by bacteria of the gastric region was generally regarded by gastroenterologists as an impossibility, due to the inhospitable environment which, through secreted acids, allegedly kept the stomach sterile.[25] Warren and Marshall, however, found a strong association between two kinds of peptic ulcers and what seemed to be infection by a bacterium. After a struggle for having their views put to the test, Warren and Marshall were finally vindicated, thus turning an implausible or impossible entity into a central actor in gastric pathology. This required the development of different research lines, involving several specialties in biomedicine, including gastroenterology and microbiology. Identified at first as a strain of an

[25] See the contributions included in Barry Marshall (ed.), *Helicobacter Pioneers: Firsthand Accounts from the Scientists who Discovered Helicobacters*, (Carlton House: Blackwell Publishing, 2002).

already known bacterium, *Campylobacter*, and christened accordingly *Campylobacter pyloridis* and later *Campylobacter pylori*, the new bacterium would finally be recognized as an altogether different genus and renamed *Helicobacter pylori* (H.p.) in 1989.[26]

Over the decade following its successful culture, H.p. would become the subject of an increasing number of publications (Figure 1) in a diversity of journals aimed at different specialties in biomedicine and originating in a range of countries form both North and South (with a clear dominance, however, of publications form the North).

1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	**Total**
3	15	94	208	374	376	324	569	564	971	1052	1403	**5953**

Figure 1. Publications on *Helicobacter pylori*, 1984-1995 (Source: ISI, Science Citation Index)

[26] C. S. Goodwin, "How *Helicobacter pylori* acquired its name, and how it overcomes gastric defense mechanisms", *Journal of Gastroenterology and Hepatology*, 9 (Supplement 1) (1994): S1-S3. Marshall has recently edited a volume including a number of contributions on work which, according to the reconstruction proposed by the very organization of the book, opened up the path to the identification and characterization of H.p. (Marshall, *Helicobacter Pioneers*). For an useful overview of the setting and chronology of early work on *Helicobacter pylori*, see Paul Thagard, "Ulcers and bacteria I: Discovery and acceptance", *Studies in History and Philosophy of Science, Part C, Studies in History and Philosophy of Biology and Biomedical Sciences*, 29 (1998): 107-136; Paul Thagard, "Ulcers and bacteria II: Instruments, experiments, and social interactions", *Studies in History and Philosophy of Science, Part C, Studies in History and Philosophy of Biology and Biomedical Sciences*, 29 (1998): 317-342; Paul Thagard, *How Scientists Explain Disease* (Princeton, New Jersey: Princeton University Press, 1999). Beyond more general disagreements on Thagard's epistemological and theoretical commitments and on his treatment of science studies, this work and the broader project it is part of differs from Thagard's in one very important respect: its aim is not to provide a general argument on how scientists explain disease through a particular case study, but to

In 1991, four different studies established a relationship between infection by H.p. and gastric carcinoma. Further evidence on the latter led the International Agency for Research on Cancer to declare H.p. a class I (the most dangerous type) carcinogen in 1994.

By that time, H.p. had been recognized as a key factor in many gastric diseases. A major event in the path towards this recognition was the 1994 NIH Consensus Conference. On that same year, a group of specialists in gastric pathology met to update the guidelines for the diagnosis and prognosis of gastritis, stressing the central role of H.p. in most forms of chronic gastritis and associated gastroduodenal diseases:

> The discovery of *Helicobacter pylori* totally altered our concepts of etiology, as it has become apparent that infection with this organism is the major cause of nonautoimmune chronic gastritis. Furthermore, investigations of gastritis prompted by the discovery of *H. pylori* have led to the recognition of other distinctive forms, such as lymphocytic and reflux gastritis.[27]

These guidelines, known as the Updated Sidney System, were published in *The American Journal of Surgical Pathology* in 1996, and have become an obligatory point of passage [28] for clinicians and clinical researchers. In 1997, the first Maastricht Consensus Report established further guidelines for the management of H.p. infection. By

follow the ways in which a specific biomedical entity is performed through a range of situated practices and their narrative reconstructions.

[27] M.F. Dixon et al, "Classification and Grading of gastritis: the Updated Sydney System", *The American Journal of Surgical Pathology*, 20 (1996): 1161-1181, on 1161.

[28] Bruno Latour, *Science in Action*, (Milton Keynes: Open University Press, 1987).

the mid-1990's, and in spite of some influential but minority dissenting voices, H.p. was well-established as a central actor in gastric pathologies. Its association, as shown by epidemiological studies, with chronic gastritis, peptic ulcer and gastric carcinoma, was regarded by most researchers and clinicians in the area as a settled question, and treatment of infection by H.p. had been successfully managed through the use of antibiotics. In 1997, *Nature* published the first complete sequence of the genome of two strains of H.p..[29] This was followed by a plethora of studies on the variety of strains of H.p. and on their respective genotypes. The latter is seen by researchers as a crucial step towards more effective strategies for the treatment of infection.

In July 2005, Robin Warren and Barry Marshall were awarded the Nobel Prize for Medicine or Physiology for their work on the associations between infection by *Helicobacter Pylori*, and common gastric diseases, such as peptic ulcer disease or chronic gastritis, as well as its role as a precondition of gastric cancer.

One of the most relevant consequences of the emergence of the new pathogen was the recognition of H.p. infection as a major health problem affecting populations in different regions of the world, more severely in Southern Europe, Africa, Asia and Latin America. Epidemiological and clinical work demonstrated how widespread infection by H.p. was in these different regions. But it also displayed a considerable range of differences in the clinical and epide-

[29] J.F. Tomb et al, "The complete genome sequence of the gastric pathogen Helicobacter pylori", *Nature*, 388 (1997): 539-547.

miological outcomes of infection by H.p. and in their geographical distribution. Throughout the 1990s, further research showed that these differences were associated with a variety of strains of the bacterium, identifiable though their diverse genotypes, and with the variable virulence of these strains.

In spite of the portrayal of H.p. as the villain in stories of gastric disease, researchers face many uncertainties as far as the question of the pathogenicity of H.p. is concerned. In fact, whereas infection with H.p. is common among different populations (even if the prevalence of the infection may vary between ca. 50% and ca. 90% depending on the region), not all carriers of the bacterium are symptomatic, and only a fraction of them end up developing serious conditions of the gastric tract. The variable pathogenicity of H.p. – a notion used interchangeably with that of variable virulence – is thus not an intrinsic property of H.p. Being infected with H.p. does not necessarily mean that symptoms of dyspepsia, gastritis or peptic ulcer disease will appear, or that those infected will be invariably at risk of developing gastric cancer or MALT lymphoma. The problem for researchers, clinicians and public health officials is neatly summarized in the following passage:

> *H.pylori* has probably been part of the normal microbial flora of humans since ancient times (...). If we assume that colonization has occurred over a long time, it is plausible that the bacterium has since adapted to fit its ecological niche in the gastric mucosa. This may have developed into symbiosis of bacterium and host, and thus *H. pylori* and the human host exist in a dynamic equilibrium, microorganisms and host signaling each other (...). Disruption of this equilibrium may influence processes such as epithelial cell proliferation and apoptosis, gastric acid secretion, and lym-

> phoid proliferation. At present, it is unknown which factors determine development of disease, and many patients remain asymptomatic, despite persistent colonization by *H. pylori*. However, these processes are multifactorial and extremely complex, involving bacterial virulence factors, host factors and environmental conditions. Each will play a role, but the relevance of individual factors as well as their interaction is not clear at present.[30]

The action of H.p. as a pathogen thus depends, according to this view, on three kinds of "multifactorial and extremely complex processes": "bacterial virulence factors", "host factors" and “environmental conditions". The outcome of the intersection of these processes is not always the development of disease, since asymptomatic patients infected with H.p. are common. Notions like "symbiosis" and "dynamic equilibrium", and explicit reference to the way the bacterium "fits" its "ecological niche" in the gastric mucosa hint at the existence of "normal" or non-pathological relationships between bacteria and host.

Further difficulties arise in relation with the need to identify the sources of variable virulence (or pathogenicity) of the bacterium. Is it an outcome of the variability of bacterial strains? Or does it arise from the relationships between infection with specific bacterial strains, host susceptibility and environment (such as conditions of access to sewage and clean water, for instance)? The problem was compounded, first, by the emergence, among different populations, of increased resistance to treatments aiming at the eradication of H.p. which had been widely used since the early 1990s,

[30] Figueiredo, Genotyping, Epidemiology and Clinical Relevance (cit. n. 25), 205.

with success rates of the order of 90%. This problem has been associated with strains which have developed resistance to some of the antibiotics used in these treatments. Other complications entered the picture as the flipside of successful eradication became apparent. Whereas the predictable relationship between eradication of H.p. and the decrease of pathologies like peptic ulcer and non-cardia gastric cancers has been confirmed, other diseases, like gastroesophageal reflux, Barrett's esophagus, adenocarcinoma of the lower esophagus or gastric cardia have increased "dramatically and progressively". Some of the strains of H.p., as suggested by a number of studies, may well offer some protection against the latter diseases, even if the same strains are "associated with a higher risk for diseases of the lower stomach" (Figueiredo, 2000: 206).[31] This raises the possibility that

> [b]y eliminating H. pylori to reduce risk in one group of diseases, the risk for others could be increasing. It can even be hypothesized that *H. pylori* might have other beneficial features for the host, not apparent today.[32]

The variability of clinical outcomes of H.p. infection and of H.p. eradication thus brought to the centre of the concerns of researchers and clinicians the need to understand the sources of the variable pathogenicity of the bacterium. As stated earlier, this prompted research into the variability of bacterial strains and their association with what researchers

[31] Figueiredo, Genotyping, Epidemiology and Clinical Relevance, 206.
[32] Figueiredo, Genotyping, Epidemiology and Clinical Relevance, 206

defined as host-susceptibility and environmental factors. Rather than defining virulence or pathogenicity as an attribute of bacteria, researchers set up a range of experimental and observational apparatuses which would allow virulence/pathogenicity to be enacted as phenomena.

Enacting virulence

Let us turn now to a more detailed examination of how "virulence" and "pathogenicity" (used by researchers as interchangeable terms) are enacted through specific research and clinical practices, and how they have become key aspects in the explanation of the diversity of clinical and epidemiological outcomes of H.p. infection within and between populations in different regions of the world.

Throughout the second half of the 1990s, H.p. was progressively redefined as a "worldwide population of bacterial variants, which may have different clinical impact in different parts of the globe", rather than being regarded as "a single infectious organism".[33] Host susceptibility, in turn, focused in more detail on the identification of human polymorphisms associated with mucins, the IL-1 cytosin, blood groups and the HLA system.

By the late 1990's, an important focus of research was the elucidation of the molecular structure of genes associated with virulence in different strains of H.p. and of their epide-

[33] Figueiredo, Genotyping, Epidemiology and Clinical Relevance, 171.

miological and clinical significance, which proceeded along three main lines:

- the development of methods (molecular biological and serological) for typing H.p. strains;
- the mapping and analysis of the distribution of H.p. strains across the world, their associations and relationships with epidemiological data on gastric diseases;
- the assessment of the clinical relevance of genotypes of H.p., drawing on a range of molecular biological, serological and epidemiological procedures.

Different apparatuses were available for the task of redefining H.p. as a variety of strains characterized by their genotypes and serological profiles and associated with variable clinical and epidemiological outcomes. These apparatuses include endoscopical observation of patients and sampling of biopsy material; provision of tissue samples from patients through surgical procedures; histological procedures; DNA isolation/extraction; RAPD (Random Amplification of Polymorphic DNA, also known as PCR fingerprinting), PFGE (Pulsed-Field Gel Electrophoresis), RFLP (Restriction Fragment Length Polymorphism), PCR-reverse hybridization, based on the Line Probe Assay principle; several assays used for serological analysis; and statistical analysis of data.

A number of differences between genotypes were thus identified, such as variation of gene order or variable presence of plasmids. The mechanisms underlying the diversity

of strains, including point mutation, transformation and recombination were also investigated. But the main interest of researchers was the search for genetic markers of the differential degree of virulence of different strains. Whereas genotypical characteristics can be identified through gene sequencing techniques, "virulence" cannot be performed by resorting to any single apparatus mobilized in biomedical and biological research, or in clinical or epidemiological practices. The definition of "virulence", in fact, is the outcome of a set of phenomena produced through a range of apparatuses. This involves, first, taking biopsies or other biological materials from both patients with gastric diseases associated with H.p. infection and healthy individuals. Next, bacteria are genotyped and different strains characterized. It is only after genotyping that specific genes and their allelic variants can be identified and later associated with the presence of infection in patients. The characterization of specific genes defined as virulence-associated genes is a material/discursive construction, which requires the genotyping of the bacterial strains infecting diseased patients and the identification of their allelic variants associated with infection:

> Since not all *H. pylori* infections result in the development of disease, considerable effort has been taken to identify genetic markers for the degree of virulence of different strains. This has resulted in the identification of several virulence-associated genes, which (the genes or one of their specific allelic variants) are often present in *H. pylori* strains isolated from patients with disease, but are mostly absent in strains from healthy individuals. Thus, the term

> virulence-associated genes is largely based on clinical and epidemiological observations".[34]

The virulence-associated genes thus identified include the following:

- *vacA*, which encodes a toxin damaging epithelial cells through the formation of vacuoles; a distinction is made between *s* and *m* regions of the gene, based on allelic variation, allowing the identification of several types and subtypes;
- *cagA*, a gene whose presence is considered a marker of a *pathogenicity island*, a multigenic region associated with virulence;
- *iceA*, induced by contact with the epithelium; there are two allelic variants, but their function is not clear;
- *babA*, which is associated with binding to blood-group antigens; two allelic variants are known.[35]

Each of these genes is thus linked to specific effects on cells (effect of a cytotoxin through formation of vacuoles that damage epithelial cells; induction by contact with epithelium; binding to blood-group antigens…). For the purpose of enacting variable virulence or pathogenicity, multiple strains are identified through their genotypes and these, in turn, through the presence or absence of specific allelic variants of the genes of interest.

[34] Figueiredo, Genotyping, Epidemiology and Clinical Relevance, 23.
[35] Figueiredo, Genotyping, Epidemiology and Clinical Relevance, 23-25.

Finally, the distribution of strains defined by specific genotypes is characterized through epidemiological studies. In fact, the expression "virulence-associated genes" is "largely based on clinical and epidemiological observations".[36] "Virulence" emerges from the practices which actively produce the boundaries between bacteria and hosts or of bacterial strains of variable infective capacity.

The external boundaries of a phenomenon are not defined once and for all. They are established through the intra-actions constitutive of the material/discursive practices associated with each apparatus or the intra-actions of apparatuses that produce local intelligibility. Patients may thus be considered as part of the phenomenon of genotyping, in so far as bacteria are obtained from biological materials, such as biopsies, taken from patients. Similarly, the definition of the strains of interest and of the appropriate methods for genotyping are closely linked to the identification of clinical effects and to the epidemiological distribution of infection and related pathologies. Tables, charts and maps are drawn to enact "virulence" and "virulence-associated genes" as objects of scientific work and discussion, through practices constitutive of the entangled apparatuses of biomedicine.

Apparatuses: PCR-reverse hybridization-LiPA

PCR-reverse hybridization-LiPA is a procedure favoured by researchers to enact H.p. genotypes and virulence-

[36] Figueiredo, Genotyping, Epidemiology and Clinical Relevance, 23.

associated genes, and we shall examine it in some detail here. It is based on "the simultaneous amplification of multiple genomic fragments" and is "particularly suitable for standardized epidemiological studies". Its high sensitivity to "simultaneous detection of multiple strains" makes it an appropriate technique for dealing with instances of co-colonization of a patient's gastric mucosa by different strains of H.p.[37] It is noteworthy that this technique is recommended by researchers because of its appropriateness for clinical and epidemiological studies, and not simply for its reliability or efficiency as a molecular biological tool. Its use made it possible to work directly on biopsies, thus avoiding the effects of selection of microorganisms associated with bacterial cultures (Interview with researcher).[38]

PCR-reverse hybridization is described as a “method … based on the simultaneous amplification of multiple genomic fragments”, and using non-specific PCR primers, “aimed at conserved sequences, flanking polymorphic regions of interest”.[39] The fragments thus obtained, after amplification,

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[37] Figueiredo, Genotyping, Epidemiology and Clinical Relevance, 28.

[38] This particular apparatus thus displays features of what Keating and Cambrosio, *Biomedical Platforms* (cit. n. 5), define as a biomedical platform. See the last section for further discussion.

[39] PCR (Polymerase Chain Reaction) is a technique developed during the 1980s for amplifying (making copies of) particular DNA sequences, which has become a routine procedure in molecular biology and forensic laboratories. A primer is a “short, preexisting polynucleotide chain to which new deoxyribonucleotides [DNA] can be added by DNA polymerase”, an “enzyme that effects the replication of the DNA fragment between the two primers on the ends”. Daniel J Kevles and Leroy Hood, eds., *The Code of Codes: Scientific and Social Issues in the Human Genome Project* (Cambridge, Massachusetts: Harvard University Press, 1992). On the invention and development of PCR, see Paul Rabinow, *Making PCR: A Story of Biotechnology*, (Chicago: University of Chicago Press, 1996).

are analyzed through an assay known as LiPA (Reverse hybridization-Line Probe Assay), performed in one step:

> This assay comprises a nitrocellulose strip, carrying oligonucleotide probes, which are immobilized as parallel lines. The design of the probes permits highly specific hybridization of PCR fragments under stringent conditions. Consequently, reverse hybridization allows detection of single nucleotide mismatches between probe and PCR fragment. This method is easy to use, since it requires only one PCR and a single hybridization step to obtain a multiple parameter result.[40]

Through the performance of LiPA, particular marks are left on a body – defined in a broad sense, as Barad suggests –, in this case a nitrocellulose strip, which are one with the materialization of a phenomenon, variable genotypes of H.p. PCR-LiPA, is "particularly suitable for standardized epidemiological studies", since it allows the genotyping of large numbers of isolates, and its high sensitivity makes it an important procedure for the identification of situations of co-colonization by different genotypes through the simultaneous detection of multiple strains. This is the case even when these different genotypes account only for a small part of the bacteria infecting the patient.[41]

PCR-LiPA as an apparatus is composed of a PCR device; non-specific primers; DNA fragments from bacteria, obtained from specimens of biopsies or surgically removed tissue from patients; a nitrocellulose strip carrying oligonucleotide probes; a human agent operating PCR and performing the assay; laboratory equipment for the performance of

[40] Figueiredo, Genotyping, Epidemiology and Clinical Relevance, 28.
[41] Figueiredo, Genotyping, Epidemiology and Clinical Relevance, 28.

the assay. The procedure generates a differentiation/boundary between object – genotypes of H.p. – and observational agency – instruments, materials, human operators. The boundaries of the phenomenon, however, are not defined once and for all. One could include in it the patients providing the biological materials; the different materials, instruments and humans that intra-act in practices such as surgical procedures, endoscopies and biopsy sampling, histological examinations, DNA isolation and extraction. Different spaces could be include here as well, from the operating rooms to the lab benches where histological procedures, DNA extraction and processing are performed, as well as computers, statistical software packages, maps and other inscription devices for accounting for clinical and epidemiological outcomes.

Let us go back for a moment to PCR-LiPA: which "differences that matter" are established through the intra-actions constituting this apparatus, thus giving rise to new objects? Again, we should not forget that there is no intrinsic distinction between object and phenomenon. It is through the performance of PCR and the use of a set of primers aimed at the regions of interest in the bacterial genome that specific genes are "detected" ("cut" from other genomic material) and amplified for further analysis.

LiPA performs a further differentiation, through the enactment of what researchers describe as the "mosaic struc-

ture" of the genes, making available for analysis variable alleles, the cut performing now these genes as objects.[42]

Virulence-associated genes are thus defined through a specific "cut" between object and agencies of observation/experimentation, performed through an apparatus. Objects are recognizable through the marks that are left on their surroundings by the intra-actions constitutive of the apparatus, as Barad and Rouse notice. These marks become, in turn, a measuring apparatus, measuring not some property of the object itself, but of the phenomenon the object is part of. The measurement or, more generally, the evaluation of virulence or pathogenicity can thus be carried out through specific effects of the object (in this case virulence-associated genes) on devices such as a nitrocellulose strip carrying oligonucleotide probes.

Concluding remarks

The framework presented and discussed in this paper is intended as a contribution to the ongoing efforts at the reconfiguration of approaches to the modes of existence of biological and biomedical entities and to how they are enacted as objects of knowledge and as entities making a difference in the world, a "difference that matters". It is intended to be a response to the call by Lorraine Daston and other scholars in science studies for an "ontology in motion… an

[42] For detailed information on the sequence of operations and materials involved and a description of the results, see Figueiredo, *Genotyping, Epidemiology and Clinical Relevance*, 47-50, 62-63, 69, 79-80, 148-149.

ontology that is true to objects that are at once true and historical".[43] This approach is heavily indebted to the framework of "agential realism" and to the reconstruction of "naturalistic" approaches to science studies and to the philosophy of science proposed, respectively, by feminist physicist/science studies scholar Karen Barad and by philosopher Joseph Rouse. Following Barad's lead, I have engaged in a "diffractive" way with their work. This "diffractive" reading included a wide range of contributions to the STS literature (and, in particular, to the literature on the social studies of medicine and health), as well as the biological and biomedical literature which provided the main sources for the work reported on in the previous section. In these concluding remarks, I would like to engage more explicitly with some of these contributions.

Let me briefly recall, at this point, that reading "diffractively", rather than "reflexively", entails an active engagement which excludes treating texts as reified entities, thus allowing for patterns of difference to emerge though the entanglement of readings, rather than just mirroring or juxtaposing them.

Readers familiar with the different brands of actor-network theory (ANT) will recognize some themes common to ANT and to the approach inspired by Barad and Rouse which was presented and discussed in this paper. Both approaches display a concern with following or tracing the practices that constitute (depending on the approach), a specific assemblage or apparatus productive of phenomena

43 Daston, "The coming into being of scientific objects" (cit. n. 6), 14.

and of intelligibility. But whereas most versions of ANT start from the acknowledgement of the heterogeneity of the world and describe the constitution of the collective agencies they call actor-networks as operations of making and unmaking attachments, Barad's agential realist approach treats heterogeneity as the outcome of the practices constitutive of reconfigurations of the world. It should be noted, however, that recent attempts at thinking through the ontological implications of ANT by drawing upon pragmatist philosophy and, in particular, William James's work, resonate strongly with Barad's agential realism (Latour, 2007).[44] Readers will recognize some at least some "family resemblances" of this framework with Annemarie Mol's performative approach to medical practices and to "ontological politics", with Hans-Jörg Rheinberger's account of experimental systems and the performance of epistemic objects, or with Peter Keating and Alberto Cambrosio's concept of "biomedical platforms", to mention only some of those contributions which were particularly relevant for the topic of this paper.[45]

There is, first, a strong resonance of the framework proposed here with Mol's approach to medical practices as performative of bodies, knowledges and conditions which have effects marked upon the bodies of patients and make a difference in the world. The "tactics" through which these

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44 Bruno Latour, "La connaissance est-elle un mode d'existence? Rencontre au museum de james, Fleck et Whitehead avec des fossiles de chevaux," in Vie et expérimentation. Peirce, James, Dewey, ed. Didier Debaise, (Paris: Vrin, 2007), 17-43.

45 Mol, *The Body Multiple,* (cit. n. 5); Rheinberger, *Toward a History of Epistemic Things* (cit. n. 5); Keating and Cambrosio, *Biomedical Platforms* (cit. n. 5).

different enactments of or performances are made to cohere and thus avoid fragmentation are very close to what Barad describes as the entanglement of different apparatuses, each of them generating different "cuts" between objects and agencies of observation. The phenomenon of atherosclerosis as a medical condition – to take the case studied by Mol – is thus the outcome of this entanglement. The notion of "ontological politics", in turn, as a shorthand for the performativity of medical practices and the differences they make, is a significant resource for thinking through the proposal of an ethico-onto-epistemo-logical reconfiguration called for by Barad.

Keating and Cambrosio, in turn, define biomedical platforms as "material and discursive arrangements that act as the bench upon which conventions concerning the biological or normal are connected with conventions concerning the pathological".[46] Platforms allow for the coordination of practices and for specific arrangements of instruments and programs. This concept provides, on the one hand, an useful tool for the exploration of how intra-actions of apparatuses are productive of biomedical phenomena; on the other hand, however, it seems to oscillate between the conception of platforms as being based on the intersection, interdependence or cooperation of heterogeneous actors, materials, instruments and conventions and the conception that, rather than the meeting of entities and actors inhabiting separate social worlds, "empirically speaking, they are in the same room"[47]:

46 Keating and Cambrosio, Biomedical Platforms (cit. n. 5), 332.
47 Keating and Cambrosio, *Biomedical Platforms* (cit. n. 5), 332

in other words, it is the platform that defines these entities and actors through the specific differentiations and boundaries it enacts. The second conception is closest to Barad's and Rouse's notion of intra-actions (not interactions) as constitutive of apparatuses, phenomena, objects and agencies of observation. Keating and Cambrosio's concern with regulation as a constitutive feature of biomedical platforms provide as well an empirically-grounded point of entry to the discussion of how to reconsider the specific configurations of ethics, ontology and epistemology arising from scientific practices.

Rheinberger's account of experimental systems and epistemic or technical objects also resonates strongly with Barad's and Rouse's contributions. Experimental systems may be redescribed both as phenomena and as specific instances of apparatuses, productive of certain types of objects (epistemic objects) and of agencies of observation. Rheinberger's stabilized, technical objects become, in this view, part of the agencies of observation as an effect of the "cut" established by the practices constitutive of the apparatus.

Further mutual engagement (or "intra-action") of these different lines of work through diffractive readings provides significant opportunities for a productive reconfiguration of STS or STS-informed research on the diversity of both scientific practices and of the phenomena and objects they enact. This paper has sought to offer an exploration of how time-honoured topics of both biological and biomedical research and of science studies may be approached through these reconfigurations.