cescontexto

Biographies of Objects and Narratives of Discovery in the Biomedical Sciences

The case of the *Helicobacter pylori*

João Arriscado Nunes (coordinator)
Tiago Santos Pereira
Oriana Brás
Ana Raquel Matos

Nº 02
November 2013
Estudos
www.ces.uc.pt/cescontexto

cescontexto

Propriedade e Edição/Property and Edition

Centro de Estudos Sociais/Centre for Social Studies

Laboratório Associado/Associate Laboratory

Universidade de Coimbra/University of Coimbra

www.ces.uc.pt

Colégio de S. Jerónimo, Apartado 3087

3000-995 Coimbra - Portugal

E-mail: cescontexto@ces.uc.pt

Tel: +351 239 855573 Fax: +351 239 855589

ISSN 2182-9071

Contents

Foreword..... 5
1. Introduction 8
2. The crisis of epistemology and the ontological turn in science studies..... 13
2.1. Is epistemology soluble – in the social, in ontology, in ethics, in the political…?..... 14
2.2. Pragmatism, epistemology and ontology..... 17
2.3. The return of ontology..... 19
3. Inscriptions..... 22
3.1. Introduction..... 22
3.2. The scientific article as literary technology: style, rhetoric and authority..... 23
3.2.1. "Is the scientific article a fraud?"..... 24
3.2.2. The scientific article as mediation and as narrative reconstruction..... 25
3.3. Inscribing experience in/as experimente..... 27
3.3.1. Bacterial infection and gastric pathologies: the background to the 1985 article..... 27
3.3.2. Fulfilling Koch's postulates: the 1985 article..... 38
3.3. Discussion..... 45
4. Chronicles..... 47
4.1. The approach..... 50
4.2. Helicobacter before Helicobacter, or the impossible infection..... 52
4.3. And yet..... 53
4.4. From the laboratory to the consulting room and back..... 58
4.5. Locking allies into place..... 62
4.6. "Transforming the question into a series of statements which are more certain"..... 65
5. Scientometric analysis..... 71
5.1. Introduction..... 71
5.2. Overview of Publication Trends..... 72
5.3. Key Articles, Obligatory Passage Points?..... 75
5.4. Building Networks..... 78
5.5. Field Structure..... 82
5.6. Geographical Distribution of H.p. (research)..... 93
5.7. Overview of the EHSG workshops..... 98

5.8. Building Collaborative Networks..... 102
5.9. Discussion..... 110
6. Ontological variability: performing the variable virulence/pathogenicity of *Helicobacter pylori*..... 111
6.1. Introduction..... 111
6.2. The approach..... 113
6.3. *Helicobacter pylori* and its variable ontologies..... 116
6.4. Enacting virulence..... 119
6.5. Discussion..... 122
7. Concluding Remarks..... 125
References..... 128

Foreword

The story of *Helicobacter pylori* provides a fascinating case of what the science historian Lorraine Daston calls "ontologies in motion" and of how a living organism, in this case a bacterium, is constituted as a biomedical entity and thus endowed with a history and a biography through the mutual engagement of humans (researchers, clinicians, patients...) and microorganisms. Against conventional notions of scientific entities as the outcome of a process of discovery, of laying bare the hidden existence or attributes of once and for all, fully constituted, unchanging entities, the field of science studies has brought these entities back into life, as entities existing through the changing web of attachments to other living entities, including human organisms, and to the scientific and clinical practices which address and question them through the deployment of a range of apparatuses and of actions bringing together the human and the non-human, the biological and the technological, in order to generate novel creatures endowed with previously unknown or unsuspected capacities.

This book offers an account of a key episode in one such history. It does not tell the whole story of *Helicobacter pylori* (Hp) as a biomedical entity, nor does it venture into other stories featuring Hp which reach beyond the biomedical world. The text is based on the final report of a research project completed in 2008. The report itself was drafted in a format close to that of a book. As the last chapter hints at, several "lines of flight", as Deleuze and Guattari (1980) would call them, or, in the vocabulary proposed by Michel Callon (1999), "overflows", conspired to disrupt the sense of closure associated with the word "final". Bounding the biography of Hp within its capture by biomedical research and clinical practice and its definition of a – assumedly diverse and complex – pathogen would amount to neglecting some of the most surprising directions taken in recent years by research on bacteria and, specifically, on the entity which is the central character of this book, but also by the way microorganisms, and bacteria in particular, and their place in broader ecologies of multi/interspecies encounters which have become a promising topic in science studies and anthropology (Haraway, 2008; Hird, 2009a, 2009b; Kirsey and Helmreich, 2010). These directions have not only led to further additions to the already rich and complex historical ontology of Hp as it was accounted for in this book, but it also suggested possibilities for other readings of that historical ontology.

Over the last two decades, work by epidemiologists and bacteriologists on Hp and its relation to the modulation of the human immune system, studies on the social life and collective intelligence of bacteria and on the evolutionary significance of bacteria and other microorganisms and their key roles in interspecies ecologies have led to new and exciting lines of research with considerable implications for our understanding of life and human life in particular, of anthropogenic effects on life and on its conditions, on evolution, on the meetings and coexistence of species and on current definitions of political ecology (Nunes, forthcoming).

In 2011, a sabbatical leave from the School of Economics of the University of Coimbra and the generous support of a Visiting Research Fellowship awarded by Fundação Oswaldo Cruz (Fiocruz) in Rio de Janeiro, Brazil, allowed me to dedicate most of the academic year to

an exploration of these new directions. I benefitted from the unique environment of a research institution in public health with an unparalleled experience and expertise in dealing with infection and with pathogens associated with a variety of infectious diseases, as well as their social, political and environmental implications. Different versions of what I meant to be both an extension and a new look at the biography of Hp were shared with a range of audiences including researchers and practitioners in public health, the biosciences, bioethics, science studies and the history of science and medicine. My inroads into these new directions were considerably enriched by the lively comments and discussions arising at each of these venues. This work is currently being drafted for an autonomous publication (a preliminary overview is attempted in Nunes, forthcoming). The question arose, of course, whether it would be of interest to publish the 2008 report as it stood, or whether it should undergo revisions or, at least, include an additional chapter with an assumedly provisional report on new, ongoing research. The option which prevailed was that of publishing the last version of the 2008 report, but adding a foreword which would put that work into perspective from the vantage point of the ongoing work of the Principal Investigator on Hp.

This book is thus published as a piece of work standing on its own. But some features of it should be highlighted, as they will be subject to a re-reading in forthcoming publications drawing on more recent work by the PI.

The first of these is, of course, its focus on Hp as a pathogen. The book provides a detailed reconstruction of the way Hp was constituted as a biomedical entity and, more specifically, as an infectious agent associated with common gastric disease. This focus allowed a reconstruction of the play of associations and dissociations through which the bacterium was endowed with this specific identity. The flipside of this approach is that other forms of defining and engaging with Hp (some of them pointed at in work published by biologists, for instance), were left out of the story or, at best, mentioned *en passant*, even if their relevance was hinted at in the Concluding Remarks.

The second feature is the reliance on a version of what is commonly known as actor-network theory as the main tool for the reconstruction of the biography of Hp. This version follows closely that offered by Michel Callon in his landmark study of the scallops of St Brieuc (in fact, the account included in this book has been often used as a pedagogical tool to introduce students to how to "do" ANT...). The question here is not whether this choice was appropriate, but rather what other accounts can be offered drawing on an alternative problematization which would include the debates and explorations beyond the contexts dealt with here, as well as new questions arising from the more recent work within the health sciences involving Hp (on a similar problem, see Law, 2002). Our option was to leave those other accounts to a separate publication and to offer to readers the last version of our 2008 report, with the understanding that it is one of a range of possible ways of accounting for the story/biography of Hp.

Finally, Chapter 6 pointed towards another line of research which, in subsequent years, and under the influence of feminist science studies and philosophy, a more sustained engagement with pragmatist philosophy and fieldwork experiences in Europe and in Brazil, was pursued in other projects led by the PI or with his participation. This line of research involved the exploration of a diversity of assemblages and apparatuses through which phenomena are constituted as matters for inquiry and collective experimentation, and how different forms of subjectivity are constituted linked to the shaping of the dispositions associated with these

assemblages. Again, outcomes of this (ongoing) line of inquiry are currently being published elsewhere.

All this being said, it is up to the reader to judge this book, hopefully not (just) on what it has failed to accomplish, but on what it may offer as a contribution to research in science studies and in the social studies of medicine and health and to opening up new directions of inquiry on multi/interspecies relations and emerging forms of the politics of life

Coimbra, November 2013
João Arriscado Nunes

References

Callon, Michel (1999), "Actor Network Theory – The market test", *in* John Law and John Hassard (eds.), *Actor Network Theory and After*. Oxford: Blackwell Publishers, 181-195.

Deleuze, Gilles; Guattari, Félix (1980), *Mille plateaux*. Paris: Éditions de Minuit.

Haraway, Donna J. (2008), *When Species Meet*. Minneapolis: University of Minnesotta Press.

Hird, Myra J. (2009a), *The Origins of Sociable Life: Evolution after Science Studies*. London: Palgrave Macmillan.

Hird, Myra J. (2009b), "Feminist Engagements with Matter", *Feminist Studies*, 35 (2), 329-346.

Kirksey, S. Eben; Helmreich, Stefan (2010), "The Emergence of Multispecies Ethnography", *Cultural Anthropology*, 25(4), 545-576.

Law, John (2002), *Aircraft Stories*. Durham, N.C.: Dujke University Press.

Nunes, João Arriscado (forthcoming), *Knowledge and Politics in the Meetings of Species:* Helicobacter *pylori and the political ecology of life*.

1. Introduction

This report offers a first comprehensive overview of the results of the Project "Biographies of objects and narratives of discovery in the biomedical sciences: the case of Helicobacter pylori", which was completed between July 2005 and June 2008.

The project was built upon two previous projects, "The social worlds of science and technology" and "Managing uncertainty in the biomedical sciences, carried out between 1995 and 2002. Both of these projects were based on ethnographic fieldwork done at IPATIMUP (Instituto de Patologia e Imunologia Molecular da Universidade do Porto), a major research institution in the field of the Health Sciences., by the Principal Investigator (João Arriscado Nunes). Throughout both projects, the PI was confronted with the central role of a micro-organism, the bacterium Helicobacter pylori (H.p.), in both the research on the biology of gastric cancer (the specific domain covered by the first project) and as a key player in attempts at managing risk and uncertainty as they were associated with gastric cancer and with its precursor lesions. On the wake of these projects, the PI found himself with a considerable amount of materials, collected but only partially processed and used for these two projects, related to H.p., to the circumstances of its discovery, to the debates over its properties and pathogenic status, over its relationship with cancer, over its genetic makeup, over the variable virulence of its different strains. Taken together, these debates suggested that H.p. might be taken as an exemplary instance of how a biological or biomedical entity can be followed all the way from its genesis as the outcome of particular operations of knowledge production generating "epistemic things" through its development towards its stabilization as a "matter of fact", and, again, as a controversial entity giving rise to debates which seem to be far from achieving closure. H.p. thus appeared to offer a particularly interesting, empirically grounded entry point into issues which have been at the centre of debates within science studies and history and philosophy of science informed by science studies, namely the recent "ontological turn" coupled with the growing concern with practices which appears as one of the most productive paths towards theoretical and epistemological renewal within these fields.

A project was thus drafted and submitted to Fundação para a Ciência e Tecnologia (FCT) for funding. Initially, the project was intended to focus on the study of changing modes of existence – or, in other words, the changing or variable ontology – of H.p., as it was successively defined through the clinical, research and epidemiological practices which enacted it and the properties associated with H.p. through these different practices. As work on the draft proceeded, we realized that the narratives through which the discovery of H.p. was accounted for were themselves crucial elements in the definition of what H.p. was and what its properties were. The work of authors such as Ludwik Fleck, John Dewey, Bruno Latour and Joseph Rouse, among others, provided invaluable insights into the development of this convergence of a focus on an "ontology on the move" (as science historian Lorraine Daston called it) of H.p. and on the narratives through which H.p. was textually enacted. These narratives included scientific publications such as articles in scientific journals, letters to the editor, review articles, consensus statements or clinical guidelines. An unique source for first-hand narratives by the discoverers of H.p., Barry Marshall and Robin Warren, was a volume edited in 2002 by Marshall, Helicobacter Pioneers. We proposed as well to draw on interviews (particularly with Marshall and Warren) as additional documents and on archival material held at the Helicobacter Foundation in Perth, Australia. Our intention was to use the accounts provided by these

documents as sources for the biography of H.p., but also as particular instantiations of the literary technologies associated with science and with the enactment of scientific objects and entities and the legitimation of statements and of particular versions of the history of a research process or of a discipline.

In its original draft, the objectives were defined as follows:

> The general objective of the project is to reconstruct the history of the identification of, the controversies over and the research on the bacterium Helicobacter Pylori as a key entity in the pathogenesis of gastric disease and its relationship to the production by key actors of narratives of research on bacteria and gastric disease as modes of establishing scientific authority and legitimacy. Specific objectives of the project are:
> - The reconstruction of the history of research and scientific controversies involving Helicobacter Pylori (H.P.).
> - The ethnographic and historical analysis of the material cultures of research on H. P. and of clinical and epidemiological work related to it as practical "performances" of H.P. as a biomedical entity.
> - The mapping of H.P. research (actors, institutions, themes) and its evolution over the last two decades using scientometric procedures.
> - The analysis of narratives of research and discovery and their contexts by key actors in the field.
>
> The project was organized in four work packages:
>
> 1. Scientometric mapping and analysis of the field of research on H.P. and its evolution
>
> 2. Analysis of the material and textual enactments of H.P., controversies and narratives of discovery
>
> 3. Writing of report and preparation of preliminary draft of book
>
> 4. Dissemination activities

The project was submitted in 2004. Although it was approved for funding, the amount awarded underwent a significant reduction. As a consequence of having more limited resources than the ones expected, we had to revise the allocation of labour to the different tasks, suppress some of these (such as a field trip to Perth, in Australia, for archival work at the Helicobacter Foundation and interviews with Marshall and Warren), or replace them by others which would be within our budgetary constraints. We thus decided to concentrate on three main topics: the initial set of episodes giving shape to what is commonly described as the discovery of H.p. by Barry Marshall and Robin Warren, and its reconstruction through different types of accounts; the process through which H.p. became the rallying theme for an international network of researchers; and research on the virulence of H.p. as an instance of the enactment of its ontological variability. Resources were reoriented to extensive documentary research, in libraries in Portugal, France, the UK and the United States, as well as through online resources. Ethnographic materials from previous projects were re-examined and reworked, and additional fieldwork was carried out at IPATIMUP. A field trip was made to Istanbul, to attend the Annual Workshop of the European Helicobacter Study Group, the most important international research collective in the field, where the PI was able to carry out interviews with several key actors and have a conversation with Barry Marshall. Although Marshall declined to be

interviewed on the subject of the discovery of H.p – referring back to his account in Helicobacter Pioneers as his definitive statement on the subject –, he provided precious information on topics such as the relationship with the pharmaceutical industry or his more recent work on the use of H.p. as a carrier of vaccines.

The project started in July 2005. On that same month, Marshall and Warren were awarded the Nobel Prize for Medicine or Physiology for their work on H.p. and its relationship with common gastric diseases. The newly enhanced visibility of things related to H.p. generated a plethora of materials published in the media and circulated on Internet which we tried to locate and collect. The sheer amount of material gathered made it impossible to deal with this material on time for it to be included in this report. We intend to use it for futurepublications.

Throughout the completion of the project, we stumbled on some unexpected obstacles. Some of the key published materials proved surprisingly hard to find, although we finally got hold of them, through access to the impressive collections of Countway Library, at Harvard University The collection and treatment of bibliometric information, too, proved to be a far tougher task than we had anticipated. First, we had to rely on additional human resources to fulfil that task. Locating the information on available databases, converting them into an usable format for the purpose of the project, reconciling information contained on different databases, processing it and turning it into indicators, tables and graphs, experimenting with different types of software and finally selecting and displaying the information to be included in the report was a time- and labour-consuming endeavour, beyond the expectations of the research team. The extension of this work to the analysis of the networks of co-authorship and collaborations based on two data bases on the participation in the Annual Workshops of the European Helicobacter Study Group compounded this effort. We were lucky to have a specialist in network analysis skilled in the use of mapping *software*, Sandra Carvalho, volunteering to help us at the final stages of our work. Only a limited part of this work, however, made its way into this report. We intend to pursue the exploration of this material in future publications and as part of the ongoing preparation of the draft of a book, which we expect to submit to an international publisher within two years.

The tasks relating to Work Packages 1, 2 and 4 were accomplished, though with some deviations from the original proposal, due to the necessary adjustment of tasks to resources and to the volume and complexity of the materials gathered. The additional ethnographic fieldwork was useful mostly for clarifying or specifyng some aspects which had been less prominent in previous work by the Principal Investigator.

As for Work Package 4, some of the tasks proposed initially had to be dropped, such as the organisation of an international conference, due both to budgetary constraints and difficulties in reconciling the busy schedules of some of the main speakers to be invited. We benefited, though, from the kind invitation of the European Helicobacter Study Group to attend its 2007 Workshop in Istanbul, which allowed the Principal Investigator to engage in some challenging dialogues and debates with participants, as well as to conduct interviews and observation of the major scientific meeting involving the international H.p. research community.

Both the production of CD-rom and DVD material on H.p. and its history and the creation and management of a *website* could only be partially fulfilled, since the amount of time and resources necessary for the full accomplishment of these tasks require that they be pursued after the closing of this project.

Wheras the objectives related to participation of the research team in international and national scientific conferences and meetings were successfully met, the protracted processes of

submission and approval of publications in peer-reviewed journals introduced a deviation into the initial schedule. We are currently in the process of preparing a series of papers for submission, which we expect to have published within the next two years.

Finally, a word is in order on the structure of this report. Chapters 3, 4 and 6 report on the work corresponding to WP 2, and Chapter 5 on that carried out under WP 1. Each chapter stands on its own, so that readers will (hopefully) be able to read them as self-contained stories. To the "substantive" chapters, we have added a theoretical discussion of the approach underlying the project (Chapter 2) and a brief summary of the main conclusions of the project and future directions for follow-up research. We have thus experimented with different ways of organizing, analyzing and presenting data and with different types of accounts. There are overlaps and some redundancy across chapters, as readers will notice while moving from one chapter to the next, but the accounts we offer provide, at least we so expect, a sort of instantiation of one of our central arguments: the use of different ways of accounting for a process like the making of a biomedical entity help to shed light on the role of the different genres mobilized by actors to narrate their work and their achievements in enacting the variable or "moving" ontologies of that entity.

Over the course of this project, we have incurred many debts, both intellectual and related to logistic and material help. We would like to thank, first, the Center for Social Studies of the University of Coimbra for hosting this project and offering excellent working conditions to all members of the team. IPATIMUP, and in particular Professors Céu Figueiredo and José Carlos Machado, provided precious information, materials and international contacts, as well as opening up their laboratories to the PI. We benefited from access to the library collections of the General Library and the School of Medicine of the University of Coimbra, the Countway Library at Harvard University (thanks to the help of Peter Galison and Alan Brandt), the École Supérieure des Mines de Paris and the Welcome Institute for the History and Public Understanding of Medicine, in London. Many colleagues generously accepted to discuss different aspects of our work or offered advice, among them Alberto Cambrosio, Carlos Sonnenschein, Madeleine Akrich, Vololona Rabeharisoa, Pascale Bourret, Ilana Löwy, José Carlos Machado, Céu Figueiredo, Douglas Allchin, Peter Taylor and Francis Mégraud. Professors Manuel Sobrinho-Simões, Leonor David and Fátima Carneiro, all of IPATIMUP, introduced the PI to the debates and work on H.p. and generously gave of their time and opened their laboratories to ethnographic research which has been going on for over a decade and through three projects. The European Helicobacter Study Group (ESHG) kindly invited the PI to attend their 2007 Annual Workshop, in Istanbul, and to be one of the keynote speakers at that event. In Istanbul, a preliminary version of some of the findings of the project was shared with an audience which included most of the main characters of the stories told in this report. On the occasion, the PI conducted interviews with the Secretary of ESHG, Prof. Francis Mégraud (who also kindly shared a data base on the participation in ESHG workshops from 2002 to 2005) and an unpublished paper on ESHG Workshops), Adrian Lee and Colm O'Morain and held conversations and discussions with many of the participants.

Presentations of the project or of preliminary results were presented at different national and international scientific meetings. Besides the already mentioned ESHG Workshop in Istanbul (2007), these included the 2005 and 2007 Conferences of the International Society for the History, Philosophy and Social Studies of Biology, held in Guelph (Canada) and Essex (UK), respectively; the 2006 Conference of the European Association for the Study of Science and Technology (Lausanne, Switzerland); the 2006 Colloquium on "The Circulation of Science

and Technology", organized by Instituto de Ciências Sociais, University of Lisbon; and the Jornadas sobre Ciências Sociais em Saúde (Lisbon, 2008). We are grateful to the audiences of these events for their many suggestions and criticisms.

Finally, special thanks are due to two persons: to Sandra Carvalho, whose collaboration and skills in the use of network analysis was crucial for the analysis reported on in Chapter 5, and who we expect to continue to collaborate with the project team on further exploration of a very rich data set which could be only partially used for this report; and to Marisa Matias, who generously dedicated time to help with the preparation of this report.

2. The crisis of epistemology and the ontological turn in science studies

> An ontology that is true to objects that are at once true and historical has yet to come into being, but it is already clear that it will be an ontology in motion. (Daston, 2000: 14)

Post-Kuhnian history, philosophy and social studies of science have often been described as having in common an engagement with the practice of science and its objects based on the investigation of its epistemological conditions – that is, of the way knowledge claims are formulated, sustained under conditions of experimental or observational tests or of controversy, circulated and validated or rejected. It can be argued, however, that this apparent convergence towards epistemology revealed a persistent "malaise", associated with the very idea of an epistemology.

Over the last three decades, epistemology as a project has been the target of sustained criticism and of a range of displacements which culminate in the recent formulation of proposals for the rejection of that project and of its associated claim of the capacity to define the criteria for establishing what counts as knowledge and how it is validated. These displacements occurred, in succession through the transfer of "epistemic sovereignty" (Rouse, 1996a) to the "social", through the recovery of ontology and, at last, through an increased attention to the constitutive normativity and to the political implications of knowledge(s) and of the practices of its (their) production.

Some would argue that we would be witnessing a "final crisis" of epistemology or, at least, its irreversible "naturalization" or "historicization". Although these are not equivalent, they have in common the assumption that epistemology would at last be liberated from the claim of being the locus of the determination of what counts as knowledge and of the criteria allowing the distinction and adjudication of truth an error. In this chapter, we discuss first the critical discourses of epistemology, with a focus on those deployed as part of the different "turns" in the field of science studies. The second part explores what we argue is a major, if not always explicitly acknowledged, influence on the "ontological turn", that of American pragmatism and, in particular, of the work of John Dewey. The next section discusses a range of contributions within science studies and "naturalistic" philosophy of science for a "new" ontology, such as those advanced by Daston (2000), Hacking (2004) – who in turn developed a suggestion by Michel Foucault -, Latour (1999, 2005) or Mol (2002). In the last section, we propose an approach to the study of the making of scientific objects – in this case biomedical entities – which draws selectively and critically on the range of contributions discussed in previous sections. We argue that the use of narratives of discovery as biographies of objects offers an alternative configuration of epistemo-ontologies.

2.1. Is epistemology soluble – in the social, in ontology, in ethics, in the political…?

Epistemology as a philosophical project cannot be dissociated from the emergence and consolidation of modern science and o f its cultural authority. If the pretension pervading different epistemological currents and projects was to establish a theory of knowledge, the outcome of these efforts was a paradoxical enterprise. On the one hand, epistemology claimed a place external to all forms of knowledge and to all practices of knowledge production in order to carry out their independent evaluation through the adjudication of their capacity to establish the difference between truth and falsehood, but also the capacity to define the criteria allowing the distinction of true and false claims. Drawing on an analogy with philosophical approaches to power – and in particular that of Michel Foucault –, Rouse (1996a) christened this stance "epistemic sovereignty". While postulating epistemic sovereignty, though, epistemology took as a model one of the forms of knowledge it sought to evaluate: science. Claiming to be a theory of knowledge, epistemology became, in fact, a theory of scientific knowledge. In fact, from an early stage on, epistemology – particularly in its more conventional empiricist, positivist or realist versions, was faced with the troubling realization that, despite its normative pretensions, its statements were rarely invoked by scientists – except in specific situations, when science had to be publicly defended against its critics. But there was more to it: epistemology often seemed irrelevant as a way of accounting for the practices of science. It will not come as a surprise, then, that, especially during the 20th century, scientists from different disciplines engaged in a range of forms of "endogenous" reflection on the practices of science and on its epistemological and social implications.[1] This "immanent" epistemology expanded mostly during the last decades of the 20th Century (Santos, 2007).

This process was matched – and mutual influences may be traced – by what some have described as the "naturalization" and historicization of epistemology. At its roots is the acceptance of the claim that the conditions under which knowledge could be produced and validated could be adequately established only if they rested upon detailed knowledge of the practices through which knowledge was produced and validated. There were two main aspects to that process. The first relates to the decomposition of philosophy of science and of knowledge into specialized philosophies, associated with specific disciplines or areas of knowledge, elaborated through tight links with practices and debates within those disciplines and areas. The compatibility of philosophical statements with statements produced through scientific practices became a key criterium for the assessment of those philosophical statements. A particularly interesting instance of this approach is to be found in the philosophy of biology (Callebaut, 1993). The second aspect is related to the development of sociological and historical approaches to the study of the topics and concepts of epistemology. "Epistemography", as historian Peter Dear called it, thus sought to scrutinize, through empirically-based studies, the génesis and

[1] See the exemplary case of Nils Bohr, who described his reflections as "philosophy-physics". For a discussion, see Barad (2007), especially Chapter 3.

transformation of those topics and concepts as they were deployed and practically accomplished in the production of scientific knowledge and in the debates and controversies through which that knowledge was validated or rejected.[2] Science studies, in both the different versions of the Sociology of Scientific Knowledge (SSK) and in the set of approaches Taylor (2008) gathers under the label of "heterogeneous construction", have produced, over almost three decades, an impressive body of work which provided a significant empirical base and theoretical contributions of great relevance to the "naturalized" philosophies of science. This inflexion of approaches to epistemology was accompanied by the growing visibility of epistemologies labelled as constructionist or constructivist. This corresponded to a displacement of epistemic sovereignty to the social (which was defined in different ways by different approaches). The history of the sciences inspired or influenced by SKK, in turn, demonstrated the impossibility of defining criteria for the evaluation and validation of knowledge claims unless they are anchored in particular historical contexts and situations. Concepts such as truth and error, objectivity and subjectivity, observing and experimenting, describing and explaining, measuring and calculating thus came to be endowed with variable meanings and to be used in different ways, all context-dependent. A major consequence of these studies was the demonstration that the production of scientific knowledge involves a heterogeneous range of actors, forms of knowledge and contexts, and that the separation of science from its "others" (common sense, local or practical knowledges, indigenous knowledges, beliefs – including religious beliefs -, philosophy or the humanities) always involves some kind of boundary work and its stabilization requires some form of institutionalization of the differences between science and opinion, science and politics or science and religion (Gieryn, 1999). The demarcation of science from non-science is thus a contingent process, not a separation decreed once and for all by some instance of epistemic sovereignty.[3]

Feminist criticism had a prominent role in this process as well. Its contributions appeared both within different scientific disciplines and within the philosophy, history and social studies of science. Feminist approaches allowed, in a first moment, the identification of male biases both within epistemology and as constitutive theories and substantive knowledge within a range of disciplines. The influence of feminist critique was mostly visible, at first, in relation with biology and medicine.[4] Subsequently, the influence of feminism was considerably broadened, in disciplinary terms (in physics, engineering, primatology or the social sciences), but mostly through a broadening of the reflection on the production of knowledge, its conditions and processes, offering key concepts widely used in science studies, such as strong objectivity and standpoint epistemology (Harding, 2004), situated knowledge (Haraway, 1991), social knowledge (Longino, 1990) or underlining the inextricability of knowledge and normativity (Longino, 1990, 2002; Clough, 2003; Barad, 2007).

A further inflection was to leave its mark on epistemological debates throughout the 1990s, this time linked to the claims of the centrality of practices in accounting for the production of

---

[2] Ethnomethodologists like Michael Lynch have proposed the term "epistopics" to refer to the study of the practical accomplishment of the concepts and categories of epistemology (Lynch, 1993, especially Chapter 7).

[3] Throughout the 20th Century, attempts were made to problematize the boundaries separating science from its "others". The work of pragmatists like John Dewey (1991a) or of the Polish physician and bacteriologist Ludwik Fleck (1979/1935), a pioneer of science studies, or the reflections by Nils Bohr mentioned earlier are among the most significant contributions to this topic produced during the early decades of that century.

[4] See Schiebinger (1999) on the relationships between feminism, the sciences, epistemology and science studies. For an overview of the most significant contributions up to the mid-1990s, see Keller and Longino (1996).

knowledge. This "praxigraphic" orientation (Mol, 2002) generated na impressive body of research focused on the activities of scientists, engineers, physicians and other producers of scientific and technical forms of knowledge, thus boradening and transforming in significant ways the pathbreaking contributions of so-called "laboratory studies" from the 1970s and 1980s. The "praxigraphic" or "practice" turn had two significant consequences, for both science studies and philosophy of science. The first relates to the debate over the notion of "practice" and, in particular, its links to the issue of normativity in scientific activities. Following a path opened up by Stephen Turner, philosophers and social scientists questioned the way scientific practices produced, in an "immanent" way, the norms that allowed them to be assessed and validated. The constitutively normative features of scientist practices was to become a central topic of the work of philosophers like Joseph Rouse (2002). Its implication was that all scientific activities produces effects or consequences which tie in scientists to the responsibility for the difference these effects or consequences make in the world. Scientists, according to this view, are inescapably co-responsible for these differences. Some authors, like Annemarie Mol and John Law, even proposed the concept of "ontological politics" to refer to the inextricability of the cognitive, material and normative implications of scientific activities and, more generally, of all forms of knowledge production. The question of normativity was thus brought to the center of debates on science and technology, concurrently with broader discussions, often led drawing on the vocabularies of ethics and politics.

A second consequence was the "return" with a vengeance of ontology as a central concern of science studies and the philosophy of science. The discussion of ontology seems to be oriented, above all, towards how knowledge, science and technology produce new objects, entities and relations which make a difference in the world. A step which was explicitly taken by some authors was to advocate either the abandonment or, at least, the secondary role of epistemology in relation to ontology. The former position was taken, for instance, by the feminist philosopher Sharyn Clough (2003). More recently, authors like Joseph Rouse and the feminist physicist Karen Barad, even though the back many of the criticisms advanced by Clough, have taken a somewhat different route, which consists of searching for possible reconfigurations of epistemology, ontology and ethics. Barad's contibution is particularly interesting in the way she recovers and broadens Nils Bohr's project of a "philosophy-physics", as part of a "diffractive" reading of a range of contributions from feminism, post-structuralism and science studies.[5] Barad's "ethics-onto-epistemo-logy" is probably the most radical version of what could be described as the "internal" critique of epistemology as a project (Barad, 2007). The "naturalism" advocated by Rouse (2002, 2004), in turn, rests upon two postulates he regards as indispensable to any "robust" philosophical naturalism: a) no arbitrary philosophical restrictions should be imposed on science; b) all explanations based on supernatural or "mysterious" forces should be discarded. The second postulate makes it a problem to broaden this brand of naturalism to other practices of knowledge production beyond the scientific. How does one determine what counts as "supernatural" or "mysterious" within a given form of knowledge? If it is assumed that these terms could be defined drawing on how scientific

[5] Diffractive reading, originally proposed by Donna Haraway (1997), differs from reflexive reading in the way it confronts readings from diverse positions in order to produce differences that matter, in the double sense of signifying and materially transforming the world. This reading, like any process of knowledge production, is thus a form of semiotic-material practice. For a detailed presentation and discussion of this approach, see Barad (2007) and the thoughtful commentary by Rouse (2004).

knowledge understands them, then it would be impossible to analyse in a "naturalistic" way any practice which explicitly invoke entities thus regarded and which place the latter at the core of their descriptions or explanations of the world. Other proposals, such as those advanced by Bruno Latour (1991, 1996) or Isabelle Stengers (1997) seem to go considerably further in postulating the symmetrical consideration of different worldviews and modes of knowledge and the need to interrogate the terms in which they define the entities and processes which make up the world. [6]

An intriguing feature of this discussion is the, at best, discrete allusion to one of the most original and pathbreaking treatments of both epistemology and ontology in the philosophical literature of the 20th Century: American pragmatism and, in particular, the work of John Dewey. This absence is all the more surprising since the "turn" away from the centrality of epistemology, both in the form of a return to ontology and an emphasis on practices has been articulated in a sophisticated way by Dewey, namely in his major work Logic: A Theory of Inquiry. What we would like to suggest is that pragmatism is an influence that pervades this discussion, even if unacknowledged – in both senses of the word – by participants. Our own approach to the "new ontology" called for by Daston is heavily influenced by Dewey. Before going on to discuss this approach, we shall look more closely at Dewey's contribution. We are aware, of course, of the situatedness and partiality of Dewey's approach, as Paul Rabinow rightly pointed out (Rabinow, 2003, 2008). Like Rabinow, though, we regard Dewey as a crucial resource in responding to the call for an "ontology in motion.

2.2. Pragmatism, epistemology and ontology

Pragmatism as a philosophical current is often described as the only original form of philosophy ever produced in the United States. It is commonly described as arising from the meeting of European philosophical traditions with the peculiar conditions of the building of North American society.[7]Pragmatism was dominant in North American philosophy from the turn of the 20th Century until its retreat, from the mid-1950s on, by analytical philosophy. Knowledge and science are core themes in the histories of pragmatism. Classical pragmatists – Charles Sanders Peirce, William James and John Dewey – dedicated many pages to the discussion of the conditions under which knowledge – and scientific knowledge in particular - was produced and validated. Peirce's idea of community even takes the community of the producers of scientific knowledge as its model. James offered an original approach to the questiono f the diversity of the modes of knowing and their relationship to experience. Among pragmatist philosophers, Dewey was the one who made the most relevant contributions to reflection on the social conditions of what he named inquiry, the process of active engagement with the world through the construction of various forms of knowledge and experiences associated with collective activities the ways of investigating which shape "intelligent strategies to solve problems", be they practical problems (associated with the many situations of daily life), or

[6] This "naturalist" approach has been the target of a different type of criticism by Steve Fuller (2000). According to Fuller, the fragmented vision of science arising from naturalistic approaches is an obstacle to the building of forms of governance and accountability in science based on anything other than the "immanent" normativity of the various scientific practices. Interestingly, the project of a "social epistemology", advocated by Fuller and set out to fight against fragmentation, ends up postulating another form of epistemic sovereignty, based on political or citizen control of science. Fuller's arguments should nonetheless be taken seriously, since it highlights some of the problems associated with the governance of science.

[7] For alternative histories of pragmatism, see West, 1999, and Pratt, 2002, and the discussion in Nunes, 2007.

theoretical (like scientific problems), problems related to "facts" (like describing an entity or process) or related to "value" (what to do in a given situation) (Dewey, 1991a). In Dewey, we find the most emphatic formulation of the continuity of the different modes of knowing associated with a variety of forms of collective experience and social life.

Depending on the commentator, the contributions of pragmatists to the theory of knowledge are sometimes read as an "anti-epistemology", which postulates the impossibility of approaching knowledge in any other way than through its mutually constitutive relations with the the experience of the world and with the conditions of engagement with latter within various communities. Alternatively, these contributions may be read as an original conception of epistemology. The first interpretation seeks support in the criticisms Dewey made of epistemology at different moments of his long and prolific intellectual life, since his early denounciation of "that well-documented variety of intellectual tetanus called epistemology" (Dewey, 1977) to his attack on the "epistemological industry", of epistemology as speculative and self-referential activity, consisting of the discussion of concepts with no reference to the processes occurring in the world and to the subjects of those processes (Dewey, 1991b). The latter interpretation, of pragmatism as proposing an original approach to epistemology, rests upon the interest recurrently shown by Dewey in the investigation of the processes of knowledge production, of the relationship between knowledge and experience and of how knowledge is validated, which are at the centre of some of his most influential works, namely Logic: The Theory of Inquiry, from 1938.[8]

Anyway, and if we accept that a pragmatist epistemology exists, the features it displays are substantially different from those exhibited by the currents which dominated epistemology for most of the 20th Century. In fact, this interpretation has sometimes led to an understanding of that alleged originality contrary to the pragmatist project. The idea that the whole of social life (including art, religion and politics) can be interpreted through a vocabulary "borrowed" from science and epistemology – and even though hat is not the position held by Dewey – would have the paradoxical effect of allowing conventional epistemologists and self-proclaimed defenders of science and rationality to enlist him as one of "theirs", or alternatively, led to the charge of "scientism" by critics of dominant currents of epistemology.

It will be interesting to recall, even if briefly, the central tenets of pragmatis philosophy, especially in respect to knowledge:

- The pragmatic maxim (Peirce, 1992: 132) postulates that an object (or entity) can be defined by the set constituted by its effects, in other words, by what it does, as James would say. The implication is that objects and entities have no essence, their definition may change as new effects are known. Two consequences follow for the specific case of scientific practice. The first is that a scientific object or entity is defined by its effects, that is, by what is does when put to specific trials (Latour, 1999), or by the different ways it "matters" (Barad, 2007) or by the differences it makes in the world (Mol, 2002). No scientific object is a given" or pre-exists the trials that allow its effects to be known. Rheinberger's "epistemic things" (1997) may thus be read, in a pragmatist key, as objects whose effects may be knowable through specific assemblages, including experimental or observational systems. The second is that the full range of effects is never known once and for all, since additional effects may result from further trials.

[8] For a discussion of what a pragmatist epistemology inspired by the work of John Dewey may look like, see Hickman (2001).

This is one possible way of defining an "ontology on the move" (Daston, 2000) or a historical ontology Hacking, 2002).

- For Dewey, if a thing is what it does, knowledge of things has to be the outcome of procedures which are experimental in the broad sense – trials, as Latour would call them. Dewey called this experimental engagement with the world inquiry – "the controlled or directed transformation of an indeterminate situation into one which is so determined in its distinctions and constitutive relations that it converts the elements of the original situation into a unified whole". The defined situation emerging from this activity is the result of an operation which transforms elements of a situation open to a diversity of interpretations, but also to diverse futures, creating what Dewey calls a new "universe of experience" "universo de experiência" (Dewey, 1991ª: 108). The process of knowledge production, according to Dewey, takes place through different types of collective activities, which, as a whole, shape what he describes as "ways of investigating" or a "set of intelligent strategies to solve problems" (Dewey, 1991a, 1991b).

- "Pragmatic" means, to the same author, that consequences "work […] as necessary tests of the validity of propositions as long as those consequences are instituted in an operational way and are such that they allow the specific problem that elicited those operations to be solved" (Dewey, 1991a: 4).

-The notion of truth, in this perspective, is associated with what Dewey defines as "warranted assertibility", i.e., as statements or claims which are justified and always susceptible of revision (Dewey, 1991a, 1991b).

2.3. The return of ontology

The influence of pragmatism's different currents within science studies and the history and philosophy of science has not always been explicitly acknowledged. In fact, it would be more accurate to speak of something like Wittgensteinian "family resemblances to account for some striking convergences in successive "turns" in science studies over the last three decades, which, beyond their often discussed differences, display concerns which are not far from those which moved the classical pragmatists. Early work in the sociology of scientific knowledge, in ethnomethodology and in laboratory studies emphasized approaches to the topics of epistemology as empirically-based accounts of how they were enacted in specific practices and statements. "Epistemography" (Dear, 2001) or "epistopics" (Lynch, 1993) were the terms used to describe this empirical turn to explore conventional topics of epistemology such as truth, experiment or observation. Later approaches, pioneered by ethnographic studies of laboratories, brought to the fore the practices, the active engagements of researchers with the world and the co-production of knowledge about the world and the objects and entities which were the subject of that knowledge. This "practice turn" was later expanded into a "praxigraphic turn" (Mol, 2002), whereby attention was focused on how practices (scientific, clinical, technical…) make a difference in the world through their enactment of objects and bodies. That this "praxigraphic turn" shared a lot of commonalities with reflections on the ontological status of these bodies and objects associated, among other, with actor-network theory (Latour, 1999), with its attention to the modes of existence of objects and entities was a further sign of how science studies was, this time in often explicit ways, moving towards what had been constitutive concerns of pragmatist philosophy. The rediscovery of the work of Ludwik Fleck (1979/1935) and its recognition as a pioneering, though long forgotten, contribution to science studies, was

a significant aspect of this emerging intellectual landscape. Even though there is no explicit acknowledgment, by Fleck, of any intellectual influence from the American pragmatists, it is likely that they influenced some of the figures of the "Polish school" of philosophy of medicine, who in turn had a major influence on Fleck. In fact, Fleck's contention that scientific facts had a "genesis" ("Ursprung") and a "development" (Entwicklung") appeared as a challenge to realist epistemologies positing the ontological stability and autonomy of objects in the world which were to be "discovered" by scientific research.

More recently, historian Lorraine Daston openly took up the challenge of an inventory and scrutiny of the different ways in which an ontology that is true to both the reality and the historicity of objects can be enacted. Beyond the variety of responses to the challenge represented by the contributions to her editedvolume – with the telling title Biographies of Scientific Objects – (Daston, 2000), she attempts a first approach to the different ways in which this "ontology on the move", as she calls it, may be enacted through research. She distinguishes four ways in which this is accomplished: accounting for the salience, the emergence, the embeddedness and the productivity of objects or entities. Salience, according to Daston, "might serve as a shorthand for the multifarious ways in which previously unprepossessing phenomena come to rivet scientific attention – and are thereby transformed into scientific objects" (Daston, 2000: 7). Emergence, in turn, "posits a more radical form of novelty" (Daston, 2000: 9), not necessarily creating scientific objects anew – though this is a possibility -, but redefining their nature or, as Dewey would have it, their effects. Speaking of productivity means that "scientific objects attain their heightened ontological status by producing results, implications, surprises, connections, manipulations, explanations, applications" (Daston, 2000: 10). And embeddedness means that "[t]he persistence of scientific objects depends on the institutionalization of practices and an impressive array of apparatus", so that "[r]eality becomes a relative property, depending on the degree of its embeddedness in scuh organized sstems of techniques or instruments" (Daston, 2000: 12-13). Are we hearing echoes of Dewey in all four approaches?

Rather than mutually exclusive, these approaches meet in the active engagement of researchers with the processes and effects which are constitutive of the modes of existence of scientific objects.

Daston's path breaking proposals were a major influence in the design of this proposal, even though we did not always end up following her leads. The aim ofthe project is to engage with the processes through which a bacterium, later named Helicobacter pylori, moved from the status of a non-existent or contentious phenomenon to a stabilized biomedical fact, a pathogen associated with specific diseases. Our strategy was to trace the "moving" ontology of the bacterium through different types of accounts, treating these accounts as enactments of specific modes of existence of the bacterium, associated in turn with a range of effects, in the pragmatist sense, and freely drawing on various combinations of the four approaches proposed by Daston. We have focused on three main objectives:

- Researching different modes of enacting the bacterium through practices and controversies mobilizing biomedical researchers, clinicians, pathologists and epidemiologists as they are inscribed in particular types of accounts, such as scientific publications and first-person accounts by those involved in the work of "discovery".

• Following processes through which the bacterium which came to be named Helicobacter pylori moves from the condition of an "impossible" entity to an epistemic object, to an established biomedical fact, and, again, to a genetically diverse organism associated with variable clinical and epidemiological outcomes within different infection ecologies.

• Exploring accounts of the discovery of Helicobacter pylori as narrative reconstructions of the history of gastric pathology and gastroenterology.

A detailed description of both the materials used and a further specification of the approaches taken are presented in each chapter. Every chapter was designed, as much as possible, as a self-contained "account of accounts". This has generated some redundancy, which is unavoidable. But it affords a demonstration of possible ways of enacting the "moving" ontology of a scientific object. It should be noticed that no attempt at a comprehensive coverage of that moving ontology was intended, nor would it be viable within the constraints of time and resources available for this particular project. We have decided to select particular episodes or topics which provided what seemed to be particularly appropriate entry points for the accomplishment of the objectives listed above. Other stories and other accounts may be produced, but these are beyond the scope of this particular project.

3. Inscriptions

3.1. Introduction

In a book which has become a classic of science studies and the history of science, Steven Shapin and Simon Schaffer (1985) discuss how, in the 17th Century, the emergence of "experimental life", which is commonly associated with modern science, involved the simultaneous invention of a material technology, a social technology and a literary technology. Material technology allowed the "disciplining" and re-creation of natural processes under spatially confined and controlled conditions, in order to make possible rigorous observation, free of the biases induced by preconceptions. Social technology established the conditions of reliability and credibility of observations, including the attributes of observers and experimenters as "modest witnesses" of the "matters of fact" displayed through experiments; and, finally, literary technology allowed the "transportation" and circulation, in a rigorous and reliable way, of descriptions of experiments and of observations and the conditions under which they were performed, so as to achieve a "virtual witnessing" of experimental and observational practices.

According to Shapin and Schaffer, this was the historical moment when the particular ethos associated with modern science – steered by the ideal of objectivity which implied the possibility of observing and assessing "matters of fact" as distinctive from beliefs or opinions, and coming to an agreement on them –, offered a way of getting beyond the disagreements rooted in religious, philosophical and political beliefs. This particular ethos emerged under the specific conditions of 17th Century England, of the conflicts raging at the time and of the debates among philosophers over how to create a social and political order capable of overcoming religious and political factionalism. But it later was taken up by practitioners of natural philosophy and of its successor, science, as a condition for overcoming both particularistic conceptions of reality associated with what would be later called the subjectivity of social actors, and consolidating an ideal of objectivity whose normative force was inscribed in a durable way into the epistemological orientations dominant until the mid-20th Century, into the public discourse of many scientists and into the norms and conventions of the literary technologies through which the results of scientific work and its contributions to a discipline or topic are circulated, shared and reviewed, evaluated and certified by peers.

Historians, sociologists, anthropologists, social psychologists, political scientists, legal scholars, linguists, literary scholars and specialists in cultural studies took as their task the study of how scientific texts are produced, their attachments to situated practices of research, the conventions and rhetorical resources mobilized by scientists, the modes of reception of scientific texts, the variety of literary genres cultivated in the sciences – including research projects, reports, articles, letters to the editor, books, popular science books, editorials, commentaries, review articles, presentations in scientific meetings, public lectures, interviews, newspaper articles, press releases, advisory reports… The scientific article, in particular, was the object of a variety of approaches, including the ethnographic study of their production through the construction of chains of translations and inscriptions, from the laboratory or the field to the final published paper (Latour and Woolgar, 1986; Knorr-Cetina, 1981; Latour, 1999); the literary conventions and rhetorical resources which single out the article as a genre (Bazerman, 1988; Myers, 1990); the uses of articles in scientific work; the

dynamics of citation and co-citation and the way texts construct scientific authority and discursively constitute the phenomena they account for. In spite of criticisms from different authors and currents of the use of published texts as materials for science studies (Collins, 1975; Lynch, 1982), and of the variety of approaches to their study, their privileged status as means for making scientific activities and their results publicly accountable endows them with particular significance and relevance for historical and ethnographic studies of scientific practices and controversies (Woolgar, 1976, 1980; Latour e Woolgar, 1986; Latour, 1987, 1999; Myers, 1990; Selzer, 1993)

3.2. The scientific article as literary technology: style, rhetoric and authority

The history of the scientific article, as the most important of the literary genres cultivated by scientists, demonstrates in a privileged way the normative force of criteria which condition the display, through textual inscriptions and specific rhetorical and narrative procedures, of the relevance, rigour, consistency and robustness of the research its authors are accounting for.[9] Among the most prominent of these criteria are the need to endow the processes studied with the status of "real" characters of the story being narrated and the confinement of the researcher(s)/author(s) to the status of "modest witness(es)" of those processes and spokespersons for them (for instance, through the discussion of results). The elimination of references to the actions, speculations or beliefs of the author(s) thus contributes to restate the suspension or bracketing of biases associated with subjectivity both as they could affect the research on which the article is based and in the presentation and discussion of its results.

In spite of some variation in the features of articles across disciplines or scientific areas, it is possible to identify a set of common "core" conventions which seem to resist disciplinary fragmentation or difference. Respect for these conventions is repeatedly stated in processes of peer review and in the recommendations of editors or editorial committees of scientific journals. Among these conventions are the use of the passive voice, so that the author(s) are "disappeared" from the text, thus endowing processes or objects with the capacity to act or to produce effects or consequences. In addition, the scientific article appears as the most accomplished form of "delocating" scientific activity, of showing how the results of research can be separated form the conditions of their production and from the personal intervention of the scientists who author the text. The fixity and portability of the scientific text, as Myers (1990) and Latour (1987) remind us, allows a reconstruction of accounts of scientific work as the process of making available, through appropriate procedures, phenomena which were just lurking beneath the surface waiting to become manifest, without the interference of "foreign" factors, such as the biases associated with subjectivity-prone human agency.

Despite the robustness found in the norms and forms of the scientific article, the latter have generated criticisms and questionings in relation to their capacity to deliver what they promise: a rigorous description of scientific work, free of subjective biases. These criticisms and questionings were made both by scientists and by researchers in science studies and

[9] Some of the conventions associated with the scientific article are to be found, in different versions, in other genres, such as the letter to the editor, a frequent means of presenting statements or criticisms to be developed in longer pieces. As we shall see later in this chapter, the letter to the editor allow claims to be made at an early stage of research without the need to substantiate them in the detailed manner required of an article, to add corroborative evidence to claims by others or, conversely, to challenge them. The style of argument and presentation, however, is remarkably close to that of the article.

history of science. It is worthwhile recalling one of the early systematic criticisms of the scientific article as an account of scientific work made by a practising scientist.

3.2.1. "Is the scientific article a fraud?"

In 1963, immunologist and Nobel laureate Sir Peter Medawar read a lecture on the BBC with a provocative title: "Is the scientific paper a fraud?"[10]
Medawar's question did not address situations where a deliberate distortion of facts or interpretations occurs. It was, rather, a consequence of his belief that the scientific article provided an equivocal or wrong depiction of what scientific activity looked like.
Medawar starts with a definition of what the scientific article is – "a printed communication to a learned journal" which is the most important means scientists draw upon to make their work known (Medawar, 1996: 33). He then moves on to a description of the "traditional form" of the scientific article in the biological sciences which he believes, despite, as he himself recognizes, some exaggeration of its features, is close to reality – or, as he puts it, "there is more than a mere element of truth in it":

> First, there is a section called the "introduction" in which you merely describe the general field in which your scientific talents are going to be exercised, followed by a section called "previous work", in which you concede, more or less graciously, that others have dimly groped towards the fundamental truths you are now about to expound. Then a section on methods – that is OK. Then comes the section called "results". The section called "results" consists of a stream of factual information in which it is considered extremely bad form to discuss the significance of the results you are getting. You have to pretend that your mind is, so to speak, a virgin receptacle, an empty vessel, for information which floods into it from the external world for no reason which you yourself have revealed. You reserve all appraisal of the scientific evidence until the "discussion" section, and in the discussion you adopt the ludicrous pretence of asking yourself if the information you have collected actually means anything; of asking yourself if any general truths are going to emerge from the contemplation of all the evidence you brandished in the section called "results. (Medawar, 1996: 33- 34)

Let us leave aside, here, the fact that scientific articles across disciplines may display variable features which, in some cases, are more than variants of the structure Medawar presents. Medawar's objection to this structure of the scientific article rested mainly on the idea that it carried with it a representation of scientific activity as based upon inductive procedures, ignoring what he regarded as a well-established finding of philosophy of science, known to every scientist: the hypothetical-deductive model and the associated postulate of the distinction between context of discovery and context of justification. Popper is quoted as the final authority on the subject (Medawar, 1996: 36).

For Medawar, the value of the scientific article rested upon its being a form of literary technology (Shapin and Schaffer, 1985), which would allow the "virtual witnessing" of how "matters of fact" emerged from scientific research. In other words, Medawar supported a conception of the article as a representation of scientific activity which should remain as close as possible to actual scientific practices. Against the dominant model of the representation of scientific practice as inferential, though, Medawar suggested that another way had to be found of accounting for the operations of discovery and justification. Medawar thus seemed to share,

---

[10] Quotes are from the version included in Medawar (1996).

apparently without reservations, the position that the scientific article should be a description of the scientific operations generating the results presented and discussed, but he disagreed on what he regarded as an equivocal reliance on an inductive approach to the representation of scientific practice. The scientific article was an intermediary between the operations of knowledge production (although he might, at the very least, frown at calling it "production"…) and the sharing of those operations and their results. What gets into the article from scientists' work is what readers get. Interestingly, the only section found in the "classical form" of the scientific article which he has no objections to is the "Methods" section, precisely the one which, as has been shown by three decades of ethnographic work of scientific practices, has contributed most to establishing a vision of scientific practice "deleting" its situated and contingent features. 11 These studies demonstrated that rather than replicating – as Medawar charged them with – inductive arguments, scientific articles produce a range of effects which are constitutive of science as a collective activity, discussed in the next section.

3.2.2. The scientific article as mediation and as narrative reconstruction

For Medawar, the article should be a form of intermediation, an account of the scientist's work as it happens – and, in his view, accounting for the hypotectical-deductive procedures constituting the "truth" of scientific activity. What Medawar is critical about is of the conception of the article as a textual (and narrative, as we shall see later) reconstruction of the process of production of scientific knowledge. What for him appears as a flawed description of scientific practice may be understood – as is common within science studies – as one of the various available forms of generating inscriptions of knowledge ensuring.[11] As exemplars of these studies, see Latour and Woolgar (1986); Knorr-Cetina (1981) and Lynch (1985), their intelligibility and communicability – among pairs, in this case. But it is also a form of demonstrating reliable results and of attaching the latter to the body of knowledge and to the history of the discipline or scientific specialty. The narratives of scientific practice afforded by the article as genre are certainly amenable to criticisms from the point of view of their expected "realism", as those made by Medawar. But the question he does not ask is whether the function of literary technologies in science, and of the scientific article in particular, should actually be that of describing in a "naturalistic" mode the procedures generating the results accounted for in the text, i.e., of "transporting" into the text, with as little modification as is feasible, those procedures, the elements they mobilize and the results they produce. According to Medawar, the article should be an intermediary, allowing the passage, with no omissions, distortions or biases, of what is done within the controlled environment of the laboratory experiment or observation, to a public of "second-order" observers or virtual witnesses. As three decades of contributions to science studies have shown, however, it is possible to consider the scientific article as a specific form of inscription, driven by conventions of organization and style, whose main function is the textual construction of the associations allowing the formulation of strong or robust statements, resistant to criticism – or, inversely, to weaken, qualify or relativise competing statements. As Latour might phrase it, the article provides enumerations of the sets of entities which are associated or dissociated through certain actions and procedures. Through the mobilization of stylistic, narrative and rhetorical

[11] As exemplars of these studies, see Latour and Woolgar (1986); Knorr-Cetina (1981) and Lynch (1985).

conventions, the article allows the enunciation of strong associations of certain entities and dissociations or weak links between others. One of the most common textual resources is the hierarchization of statements according to their modalizations (Latour and Woolgar, 1986; Latour, 1987) or their degree of externality (Pinch, 1985). The article thus allows the construction of the objects and entities which will be established as facts, characterized by strong associations, and distinguish them from artefacts, characterized by weak associations. The article thus conceived is part of a machine for producing "matters of fact", drawing on elements which, not being necessarily related or associated, generate effects which impose themselves to the reader with all the force of necessity. Ludwik Fleck (1979/1935) would describe this process as one of producing active associations which, in turn, generate passive associations with all the attributes of necessity. A key point, here, is that, far from being a mere intermediary, the article displays the properties of what Latour (1999) describes as mediation, transforming and inflecting whatever is introduced into it and producing outputs which cannot be deduced in a linear way from the set of elements associated for the production of the text. It is through the strength statements are endowed with through, on the one hand, the associations they articulate and, on the other hand, the modalizations of those statements, that the latter achieve the status of statements of matters of fact. The latter will be accepted as such by the community of peers represented by editors, editorial boards and referees. Once published, these statements will be in a strong position to resist criticism and controversy.

A less discussed feature of the article as mediation is the way it practically accomplishes the narrative reconstruction of science. The notion that scientific practices are inseparable from narrative reconstruction was put forward by a philosopher, Joseph Rouse (1996), but it has earned scarce attention within science studies. Rouse's proposals may be drawn and developed for an analysis of the double narrative reconstruction performed by the scientific article: that of the research processes producing certain results in order to make the latter shareable, and that of the discipline or the specialty allegedly transformed through these processes. Narrative reconstruction aims, first, at demonstrating the relevance and reliability of the work accounted for, according to criteria shared by the relevant community of researchers and relating it to the existing disciplinary body of knowledge and literature. But the acknowledgment of the relevance of the article by peers will depend on its capacity to produce statements recognized as significant contributions to research in the discipline or specialty, or as contributions to the constitution of new areas of specialties. The narrative reconstruction performed by the scientific article coincides, for all practical purposes, with the narrative reconstruction of the research field or domain the article is contributing to. This double operation of narrative reconstruction requires the text to inscribe in an adequate way the tension between continuity and innovation upon which the relevance of the article will stand. Conventions of form (size, structure, types of claims, rhetorical resources, narrative forms) which are appropriate for the scientific article have a crucial role here. They are often the subject of long and sometimes difficult negotiations involving authors, referees and editors. The durability and robustness of each instance of narrative reconstruction will depend on the scope and strength of the associations it states. All narrative reconstructions are faced, however, with the need to make statements on strong associations compatible with plausible statements on prospects of associations whose strength will be put to the test through future research. Without this second feature, narrative reconstructions would fail to do the job of pointing towards new directions or paths of research. They would be nothing but replications

of past research. Scientific work may be described, as biologist François Jacob nicely put it, as a machine to make the future – or rather, as a machine to make futures.

The articles (and letters) analysed in detail in the next section are exemplary instances of how to bring together these different requirements and manage within the text the tensions pervading scientific work and biomedical research in particular. In the 1985 article, the commentary on and final statement of the hypothesis appears as a particularly significant moment in dealing with the aforementioned tensions and opening up a new research/clinical domain within an established biomedical specialty, gastroenterology.

3.3. Inscribing experience in/as experiment

In the following subsections, we discuss the early publications which set the stage for a paper, published in 1985, which established the matter-of-factness of the causal association of bacterial infection and a common gastric disease. The paper is of interest as well as an account of one of the most famous cases of self-experimentation in the recent history of science. Our interest in the case is not mainly in its ethical implications – although these would certainly deserve a detailed treatment, which, however, is beyond the scope of this project -, but rather in how a key move in the establishment of bacteria causing infections in the human stomach as a matter of fact was made through the use of self-experimentation and how the latter was inscribed into a particular type of account of scientific discovery, the scientific article. The article in question was co-authored by Barry Marshall and several collaborators, and published in 1985. It provides an account of how the relationship between infection by the bacterium which would later be named Helicobacter pylori and gastritis, a common gastric pathology, was established through the fulfilment of Koch's postulates, a time-honoured set of criteria for the determination of the causal link between an infectious agent and a disease. The article appears as an exemplary instantiation of the double narrative reconstruction discussed in the previous section. The link between bacterial infection and gastritis is established through the description of an experimental procedure which includes the self-inoculation of one of the authors with the putative infectious agent. The validation of the procedure is achieved through explicit reference to Koch's postulates. This allows, on the one hand, the procedure to be attached to criteria acknowledged within bacteriology, and, on the other hand, to present the work by Marshall and his collaborators as a contribution which is expected to transform current approaches in gastroenterology and to induce a reconstruction of the history of this biomedical specialty, through the display, as a scientific error, of the denial of the role of bacterial infection in common pathologies of the gastroduodenal region.

Before discussing this paper, we have to go through the sequence of publications which set the stage for it.

3.3.1. Bacterial infection and gastric pathologies: the background to the 1985 article

Let us start by a brief exploration of the background to the 1985 article. In fact, that article is one in a sequence of publications, including two letters and another article, each of them accounting for different steps in establishing the "matter of fact-ness" of bacteria as causes of gastroduodenal disease. In the late 1970s, Australian pathologist J. Robin Warren made repeated observations of the presence of microorganisms in biopsies of patients affected by a range of common pathologies of the gastric region. He identified these microorganisms as

bacteria. References to spiral-shaped bacteria in the stomach of mammals, including human beings, had been frequent since the late 19th century. But the origin of these micro-organisms and their links to gastric diseases had not been established. In 1954, Ed Palmer, a senior figure of gastroenterology, serving at the Gastroenterology Service of the Walter Reed Veteran Hospital in Washington DC, published an influential paper in Gastroenterology, the main journal in the specialty. The article, "Investigation of the Gastric Mucosa Spirochetes of the Human", registered the repeated observation of spirochetes in the stomach of various species of mammals (including humans) since the first reports by Bizzozero in 1893, which led him to undertake an extensive investigation of gastric mucosal biopsies from a total of 1,000 adults. The relative distribution of the different parts of this short (slightly over two pages of text, plus references) paper is noteworthy. The introductory part, reviewing accounts of previous observations of spirochetes, takes about half the full length of the paper. It is followed by a section ("Material and Method") starting with a lengthy and detailed description of the selection and distribution of subjects according to their status regarding gastric disease, with a control group of about one-fifth of the sample and the larger group being composed of "patients being investigated for upper gastrointestinal complaints [who were] eventually found to have a great variety of organic and functional diseases. Some were severely and chronically ill, but none was near death", and "[a]ll adult age groups were represented" (Palmer, 1954: 219).

Palmer goes on, in the same section, to describe the procedures he used, which included taking a "gastric mucosal biopsy" from each subject using a "vacuum-tube technic" and, for 180 subjects chosen at random, a second biopsy at a later date (the total number of biopsies was thus 1,180). Most of the biopsy specimens were of "the fundal type of mucosa", although the specimens were taken from "various areas of the stomach". He then gives an account of the slicing, embedding and staining (with hematoxylin and eosin) of the samples, adding that every slide was "reviewed in detail with the sole intent of demonstrating spirochetes". In order to make sure that "structures clearly appearing to be spirochetes, as described by others, were easily demonstrated", specimens from the stomach of rhesus monkeys which had been autopsied were examined, as a procedure for "familiarization" with those structures (Palmer, 1954: 219). The section on "Finding" has just two lines, matter-of-factly stating that "[n]one of the 1180 specimens was found to contain spirochetes or any structure which could reasonably be considered to be of spirochetal nature". In the last section ("Comment"), Palmer emphatically denies contestation of what he regards as satisfactory documentation of "[m]ucosal infestation by spirochetes of some normal human stomachs which are obtained at autopsy". But he provides, even if the tone is cautious, an explanation consistent with his findings based on biopsies:

> It is suggested that such infestation is an agonal or post-mortem process, and that the source is the oral cavity. If this is so, the organism represents one or more of the normally occurring commensal spirochetes of the mouth. Apparently when the stomach is involved by carcinoma or ulcer the spirochetes are retained or otherwise encouraged to remain at the diseased area during life. (Palmer, 1954: 219)

Despite the use of what Latour and Woolgar describe as type 3 statements, containing statements about other statements or modalities[12] in these passages – drawing on qualifiers such as "it is suggested", "if this is so" or "apparently", Palmer rests his case on his finding based on – as he is careful to remind – 1,180 specimens and on a careful experimental and observational design, described in a detailed and lengthy manner. The authority of what he states in the "Discussion" section" is brought back to the readers in his short and crisp conclusion (five lines), where earlier qualifications are abandoned (with one exception, when commenting on the possible origin of spirochetes observed mostly in specimens from autopsies) and replaced by type 5 statements - statements as taken-for-granted facts (Latour and Woolgar, 1986: 76):

> It is *concluded* that spirochetes are not part of the histologic picture of the human gastric mucosa in health or prior to the agony in illness. Simple contamination of the mucosal surface by swallowed spirochetes appears to be encouraged by certain gastric diseases and is common at death, but *actual* invasion of the tubule lamina and of the tissue *does not occur* in life. (Palmer, 1954: 220, italics added)

In the wake of Palmer's paper, the position among gastroenterologists that the survival of bacteria in the inhospitable environment of the stomach was at the very least unlikely, and that the presence of spirochetes (spiral-shaped bacteria) in biopsies could be explained away as the outcome of some kind of contamination, became a matter of fact and conditioned teaching and clinical practice in the specialty.

In 1983, Robin Warren, an Australian pathologist working at the Royal Perth Hospital, sent a letter to the Editor of the medical journal Lancet, a major publication in the biomedical field, published in England, with an account of his observation of bacteria on the stomach of patients with active chronic gastritis. The title of the short text is "Unidentified Curved Bacilli on Gastric Epithelium in Active Chronic Gastritis". The letter is clearly divided into two parts. The first, corresponding to paragraphs 1-4 is recognizable as a pathologist's text, describing in detail observations of curved bacilli in patients' stomachs and offering a classification of these observations. Paragraph 5 provides a transition from observation to plausible speculation on the reasons for their having been ignored in previous studies. The last two paragraphs, finally, enumerate some questions on the causes of the survival of the observed bacteria in the gastric mucosa, their identification and possible clinical significance. The text is accompanied by the reproduction of a slide with a section form a human gastric epithelium, showing, as stated in the caption, "bacteria on surface, forming network between epithelial cells" (Warren, 1983: 274).

The first sentence in Warren's letter is a call for overcoming a situation he describes as "sad": the neglect of gastric microbiology. He goes on to make a general statement which is at odds with Palmer's authoritative conclusion:

> Half the patients coming to gastroscopy and biopsy show bacterial colonisation of their stomachs, a colonisation remarkable for the constancy of both the bacteria involved and the associated histological changes.

---

[12] For an extensive discussion of the different forms of statements found in scientific texts, see Latour and Woolgar (1986, especially Chapter 2, pp. 75-85).

The next sentence offers a brief account of the observations which allowed him to make the previously quoted statement:

> During the past three years I have observed small curved and S-shaped bacilli in 135 gastric biopsy specimens. The bacteria were closely associated with the surface epithelium, both within and between the gastric pits. Distribution was continuous, patchy, or focal. They were difficult to see with haematoxylin and eosin stain, but stained well by the Warthin-Starry silver method [as shown in the figure accompanying the text].

In four sentences, Warren offers a brief but informative account of his observations - the shape of the bacilli he observed, the number of observations, the material they were made on and the parts of the stomach the materials were obtained from, how the bacilli were distributed. But he also adds a significant information: the bacilli he observed are "difficult to see" using the staining techniques drawn upon by Ed Palmer… While making no reference to Palmer's paper, Warren provides a first possible explanation for Palmer's results and for the more general failure to see the bacilli he observed in over a hundred biopsy specimens: there is a technical problem involved, which the use of an alternative – and widely-used – form of staining (the Warthin-Starry silver method) may help solve. This statement is not yet a major blow to Palmer's position. Palmer still has in his favour the authority based on his specific competences and skills as a gastroenterologist and the force of his 1,180 cases against Warren's 135. But a first breach, if a small one, has been opened in the dominant position towards the possibility of bacteria surviving in the gastric mucosa. The suggestion of using an alternative method of staining is made available to readers, and thus the likelihood of further, corroborating observations becomes more likely.

The following paragraphs provide a classification of biopsy findings which allows Warren to associate the presence of the bacilli and the occurrence of inflammation in cases classified as "Active Chronic Gastritis" (ACG). Besides the description of different anomalies observed in the biopsy specimens, Warren makes several statements which will be of consequence for subsequent research:

- There are recognizable alterations associated with ACG. Besides those found in chronic gastritis, such as the presence of more small round cells than in a normal state or superficial oedema of the mucosa, there is, for instance, "an increase in polymorphonuclear neutrophil leucocytes", and it is "unusual to find no inflammation" in these cases.

- "When there was no inflammation bacteria were rare", but the "curved bacilli were almost always present in ACG, often in large numbers and often growing between the cells of the surface epithelium". This openly contradicts Palmer's perfunctory declaration on the inexistence of what Warren is describing. The curved bacilli were not found on the surface of the mucosa, but on the epithelium beneath the mucosa, "closely spread over the surface".

- Although the bacilli and the histological changes observed in association with them could be present in all parts of the stomach, their most consistent location was the gastric antrum. The bacteria – and the associated histological changes - were most commonly found where no focal lesions, such as ulcers or carcinomas, were not present. In those

> cases, it was common to find inflammation with no bacteria occurring in the mucosa near these focal lesions.

Warren claimed that the "extraordinary features of these bacteria" were, first, that they were "almost unknown to clinicians and pathologist alike", that they were "closely associated with granulocyte infiltration" and that they were "present in about half of our routine gastric biopsy specimens in numbers large enough to see in routine histology". Rather than features of the bacteria, the second and the third would seem to be associated with then current clinical and pathological practice and with something seemingly wrong with routine histology. But it is noteworthy to underline his attribution of what would be problems in the organization and practice of biomedical activities to "features of the bacteria". Whereas the observation of biopsy specimens and histological manipulations and examinations are human practices, the agency behind the problems facing these practices seem to "reside" somehow in the bacteria and their properties (including the lack of reference, or the marginal mention of, these bacteria in "major studies of gastrointestinal microbiology"). Among these properties would figure prominently the difficulty in culturing them (the author mentions the comparable case of *Candida*, a microorganism "sometimes found in the floor of peptic ulcers) – and thus "disciplining" them through laboratory procedures, making them compliant with the aims assigned to them by clinicians, pathologists or microbiologists. A parenthetical allusion is made to a letter by Barry Marshall dwelling on this topic and published in the same page of the same issue of Lancet.

Warren concludes with two short, more speculative digressions. The first is on possible explanations for the survival of the bacteria in an acidic environment, in principle inhospitable to bacteria. His comment is tentative, and hints at the way the bacteria may find shelter in the epithelium near the neutral end of a "pH gradient from acid in the gastric lumen to near neutral in the mucosa vessels". The mucus overlying the epithelium could thus presumably protect the bacteria. The second digression is on the "identification and clinical significance" of the bacterium, which "remain uncertain". He advances the suggestion that the bacterium resembles Campylobacter jejuni when observed under a light microscope, but it resist classification using standard reference work, such as Bergey's Manual of Determinative Bacteriology (a widely used reference work). His final sentences sound like a programmatic statement which would allow further investigation of these two topics:

> The stomach must not be viewed as a sterile organ with no permanent flora. Bacteria in numbers sufficient to see by light microscopy are closely associated with an active form of gastritis, a cause of considerable morbidity (dyspeptic disease). These organisms should be recognised and their significance investigated.

As Latour (1987) has often reminded us, and as a considerable body of work in science studies has illustrated, the fate of scientific publications and the statements they inscribe are in the hands of their readers, and first of all of the authors' peers. What the will do with these statements, whether these will fade among the thousands of pages stored in traditional or electronic libraries, challenged and criticized or put to the test through their appropriation for further research or, in this case, clinical practice) is not in the hands of their author(s), although these commonly draw on a range of stylistic and rhetorical devices which may strengthen the associations they wish to make or unmake through their textual enactment. What kinds of strong statements and associations has Warren achieved to make visible in his letter, and what associations has he weakened or unmade?

The first strong statement provides an exemplary instance of what Dewey (1991/1938) called "warranted assertibility", a kind of empirically-grounded demonstration of the matter-of-factness of the existence of bacteria in the human stomach, more precisely in the gastric antrum. Warren's statements on this point open up the possibility of further observations by others which may corroborate and extend or, alternatively, raise doubts about the nature and characteristics of the S-shaped bacilli found by Warren.

The second strong statement claims an association between the presence of the bacteria and the pathological condition of patients who provided the biopsy samples for histological analysis. This does not yet amount to a strong association between the presence of bacteria and bacterial infection as a causal factor of gastric disease, in this case active chronic gastritis. But it does plausibly point towards that kind of association.

Finally, Warren makes a case for the need to further investigate the micro-organisms inhabiting the human stomach, thus explicitly challenging the common view that the stomach is a "sterile organ with no permanent flora". Barry Marshall's letter to the Editor published in the same issue of Lancet (and on the same page) is apparently a comment on Warren's, but in reality it turns out to be a complement to and an extension of the latter (Marshall, 1983). In fact, as they confirmed in later statements, Warren and Marshall had agreed to send their letters together to the Editor of the journal.[13]

Marshall starts by formulating the three questions he claims are raised by Warren's letter: why have these bacteria not been seen before? Are these bacteria "pathogens or merely commensals in a damaged mucosa"? Are they a strain of known bacteria, the campylobacters, or, as the question implies, a new species?

The three questions are, in fact, crucial for establishing the matter-of-factness of the bacteria observed by Warren and of their associations with gastric pathologies and for explaining the specific properties of the bacteria which allow them to survive in the human stomach. They are an extension and further specification of the kinds of questions raised throughout Warren's letter. But Marshall moves one step further and goes on to provide plausible responses to each of the three questions he has raised.

His first move consists of listing and commenting on a series of reported observations of bacteria in samples of gastric tissue,[14] starting with Doenges' 1938 report on the finding of spirochetes in the stomach of rhesus monkeys and humans. Doenges had identified spirochetes in 42% of 242 stomachs, but stopped short of drawing conclusions on pathological implications, because autolysis of the specimens obtained at necropsy made them "unsuitable" for any further analysis. Notice that the title of Doenges' paper, "Spirochaetes in the gastric glands of Macacus rhesus and humans without definite history of related disease" (Doenges, 1938), signals the failure to provide anything counting as evidence of a pathogenic relation between the observed bacteria and their clinical significance. In 1940, Freedburg and Barron found spirochetes in slightly over one-third of 35 "partial gastrectomy specimens", "after a long search", concluding that "the bacteria colonised the tissue near benign or malignant ulcers as non-pathogenic opportunists" (Marshall, 1983: 1273). Finally, Marshall takes up Ed Palmer's 1954 article (discussed above) and, this time, adds a significant comment: "…he did not use silver stains, so, not surprisingly, he found 'no structure which could reasonably be

[13] See Chapter 4 for another account of this episode.

[14] The volume edited by Marshall in 2002, Helicobacter Pioneers, contains a more complete account of these early observations, starting in the late 19th Century with Bizzozero. See Chapter 3, supra.

considered to be of a spirochaetal nature'" (Marshall, 1983: 1273). Marshall thus suggests that Palmer may have failed to see the spirochetes he was specifically looking for (see Palmer's statement on that in his article) because he did not use the appropriate staining technique, which should have been silver staining. This comment joins Warren's statement on the unsuitability of common staining techniques such as those used by Palmer (who is not explicitly mentioned in Warren's letter) to make the bacteria visible to the observer. Marshall concludes his overview by stating that since the publication of Palmer's article mentions to spiral bacteria had disappeared, except as curiosities, mentioned as asides in texts on other topics. Even with the wide adoption of gastrscopic biopsy, the subject was "not reopened", and the explanation given for the "bacteria hav[ing] been overlooked is that "[s]ilver staining is not routine" (Marshall, 1983: 1273-1274). Marshall thus offers an explanation for the failure to identify bacteria in the gastric region as a problem of using the wrong technological tool, in this case inappropriate staining techniques. In fact, Palmer's article, as we have seen, suggests the plausibility of this explanation. Palmer was explicitly and exclusively looking for spiral shaped bacteria. But he used a staining technique which would not allow these to become visible to the observer.

In the next paragraph, Marshall gives a summary of what was then known of spiral gastric bacteria found in other animal species, which "are thought to be commensals". They "do not cause any inflammatory response, and no illness has ever been associated with them" (Marshall, 1983: 1274). This observation seems, at first sight, to weaken Marshall's (and Warren's) case for the possible pathogenicity of spiral-shaped bacteria. But Marshall then moves on to challenge a non-explicit assumption of the comparison or contrast between animal and human studies of the topic:

> Investigation of gastric bacteria in man has been hampered by the false assumption that the bacteria were the same as those in animals and would therefore be acid-tolerant inhabitants of the fundus. Warren's bacteria are, however, shorter, with only one or two spirals and resemble campylobacters rather than spirochaetes. They live beneath the mucus of the gastric antrum, well away from the acid-secreting cells. (Marshall, 1983: 1274)

This is a key passage in Marshall's text. His challenges to previous work are not just of a technical nature. He challenges the very way of thinking that has led to what Warren called the "sad neglect" of human gastric bacteriology. First, he states that the assumption that the gastric bacteria found in humans are the same as those found in animals is "false". He then claims that the bacteria found by Warren are not spirochetes, but rather "resemble campylobacters". There is, thus, a further flawed assumption underlying most of the previous work: it was led by the search for the wrong micro-organism. Marshall and Warren, at first, were inclined to consider the newly found bacteria as a strain of *Campylobacter*, and they even christened it, in their early work, as *pyloric campylobacter*, *Campylobacter pyloridis* and then *Campylobacter pylori*. The final assignation of the bacterium to a new species would not come until several years later, after work by Romaniuk *et al.* (1987) showed that *Campylobacter* pylori was not a "true" *Campylobacte*. The final christening of the bacterium as *Helicobacter pylori* occurred in 1989. But until then, its specific mode of existence was as a (though unusual) strain of *Campylobacter*. Interestingly, it was through the observation and manipulation of the bacterium as a strain of *Campylobacter* that Marshall and his collaborators successfully cultured it and were able to describe its features and properties. The culture of the bacterium from biopsy specimens obtained form the antrum was, indeed, achieved through

"*Campylobacter* isolation techniques". Marshall goes on to describe the size, shape, and appearance of the bacteria. Interestingly, the results of the observation of the cultured bacteria and their morphology raise doubts on their classification as a strain of *Campylobacter*:

> These bacteria do not fit any known species either morphologically or biochemically. Similar sheathed flagellae have been described in vibrios but microaerophilic vibrios have now been transferred to the family Spirillacea genus *Campylobacter*. Campylobacters, however, have a single polar flagellum at one or both ends of the cell´ and the campylobacter flagellum is unsheathed. Warren's bacteria may be of the genus *Spirillum*. (Marshall, 1983: 1274-1275)

Why is classification so important? The process of classifying the "new" bacteria allows Marshall to pinpoint one of the major failures of those he is challenging. The latter expected that their shape and behaviour would be similar to that of other bacteria found in other animals or of bacteria known to be hosted by the human organism. Marshall's letter is thus a significant step towards the consolidation of the newly observed bacteria as an "epistemic thing", a material entity whose properties are yet to be thoroughly researched, but which provides a "hold" for further work (Rheinberger, 1997). Marshall's and Warren's letters thus reinforce each other as accounts of the observation of a "fact", as early moments in the establishment of the existence of human gastric bacteria as a matter of fact. But the third question raised by Marshall is not answered in this letter. His last paragraph, like Warren's, thus reads like a programmatic statement which, as we shall see, was to be followed by two key contributions in the form of articles:

> The pathogenicity of these bacteria remains unproven but their association with polymorphonuclear infiltration in the human antrum is highly suspicious. If these bacteria are truly associated with antral gastritis, as described by Warren, they may have a part to play in other poorly understood, gastritis associated diseases. (i.e., peptic ulcer and gastric cancer) (Marshall, 1983: 1275)

In a co-authored article published in 1984, Marshall and Warren presented data showing the presence of bacilli found in the gastric mucosa of patients diagnosed with peptic ulcer disease and gastritis.[15] The article, with the title "Unidentified Curved Bacilli in the Stomach of Patients with Gastritis and Peptic Ulceration" was based upon biopsy specimens of intact areas of the gastric mucosa of 100 "consecutive consenting patients" undergoing gastroscopy. Bacilli were cultivated from 11 of these biopsies. They all displayed the attributes of the bacteria previously described in Warren's and Marshall's letters published in the same journal the previous year. The bacteria "appeared to be a new species related to the genus Campylobacter" and they were "present in almost all patients with active chronic gastritis, duodenal ulcer, or gastric ulcer and thus may be an important factor in the aetiology of these diseases" (Marshall and Warren, 1984: 1312).

The article – of which an earlier version was presented to the Second International Workshop on Campylobacter Infections, held in Brussels the previous year – restates the main

[15] After the publication of the first contributions by Warren and Marshall, both before and after the publication of the 1984 article, Lancet received a number of letters to the Editor adding reports of observations of "Campylobacter-like organisms" in the human stomach which corroborated their results. See McNulty and Watson (1984); Langenberg *et al.* (1984); Thomas *et al*. (1984); Phillips *et al*. (1984); Shousha *et al.* (1984).

arguments presented in the two letters. But it moves forward in demonstrating the existence of an association between the presence of the bacteria and common gastric diseases through a specifically designed clinical experiment. It stops short, however, of the demonstration of a causal effect between bacterial infection and the conditions diagnosed in the patients participating in the research.[16]

The paper is organized in a conventional way, with a Summary, an Introduction, and sections on "Patients and Methods", "Results" and "Discussion". In the Introduction, the authors recall some of the previous references to the observation of gastric spiral bacteria, but they add an update on the new conditions arising from fibreoptic biopsy techniques, which made it possible to take biopsies of the antrum. This technique allowed Steer and Colin-Jones, in 1975, to observe gram-negative bacilli in "80% of patients with gastric ulcer". They dismissed these results, however, as probable contamination, and identified the micro-organisms as Pseudomonas, and "the bacteria were once more forgotten"… (Marshall and Warren, 1984: 1311).

It was the "repeated demonstration of these bacteria in inflamed gastric antral mucosa" that led the authors to do a preliminary study with 20 patients which demonstrated not only the presence of curved bacilli in more than half of the biopsy specimens, but also a relationship between the number of bacteria and the severity of the pathology, in this case gastritis. The study reported in the paper was "designed to confirm the association between antral gastritis and the bacteria, to discover associated gastrointestinal diseases, to culture and identify the bacteria, and to find factors predisposing to infection" (Marshall and Warren, 1984: 1311).

In the section on "Patients and Methods", details are given on the selection of the patients, informed consent and approval of the study by the Royal Perth Hospital's human rights committee. The patients were selected for those referred to gastroscopy "on clinical grounds", gastroscopy had to be considered safe and informed consent had to be given. Selection of patients was made on a consecutive basis, until a total of 100 was reached. Patients were asked to complete a "clinical questionnaire designed to detect a source of infection or show any relationship with `known´ causes of gastritis or *Campylobacter* infection". This questionnaire, based on self-reporting, replaced "a detailed account of each patient's history". It included items such as "animal contact, travel, diet, dental hygiene and drugs", rather than focusing solely on symptoms (Marshall and Warren, 1984: 1311). The option for this questionnaire was explained in the "Discussion" section: "There was no well-defined clinical syndrome associated with pyloric campylobacter", and some of the symptoms reported by patients were found in other conditions. And since most patients reported abdominal pain (as most patients undergoing gastroscopy do), this was not a very useful piece of information. The questionnaire was thus "designed to select likely sources or causes of pyloric campylobacter infection". An example is given of the kind of relationships searched for:

> For example, bacteria might have colonised patients who already had gastritis and were taking antacids, milk or cimetidine, thus impairing their 'gastric acid barrier' and predisposing them to infection". (Marshall and Warren, 1984: 1314)

[16] For details on the research, see the next Chapter.

Other possible sources of infection considered were contacts with animals (both domestic and farm), which are known to carry campylobacters as commensals or carious teeth, and similar bacteria are known to "inhabit the human mouth" (Marshall and Warren, 1984: 1314).

In addition to the questionnaire, methods included endoscopy, histopathological examination of biopsy sections and microbiological analysis. For each, a detailed description is given of the equipment used (for endoscopy) and of the materials and procedures for the processing of biopsies and the histological analysis of sections, the culturing of bacteria and microbiological analysis.

Two comments are of particular interest here. Both hematoxylin and eosin and Warthin-Starry silver stain were used for the histological analysis of biopsy sections. It should be recalled that in previous publication both Warren and Marshall commented on the use of the first technique as being a plausible cause of the overseeing of the bacteria in earlier work. It was used, in this case, to allow sections to be "graded for gastritis" and classified according to their status as normal, with rare presence of inflammatory cells; normal, with presence of lymphoid cells but within normal limits and no other evidence of inflammation; chronic gastritis; active chronic gastrites.

The second technique was used to examine sections for "small curved bacilli on the surface epithelium" and, again, sections were graded according to the number of spiral bacteria present and their distribution. The two techniques were thus used for different purposes: examining tissues and searching for the presence of bacteria.

The second comment relates to the culturing of the bacteria. Again, the procedures used are those usual for *Campylobacter*: tissue smears were Gram stained, then examined for the presence of "curved bacilli resembling Campylobacter", then processed for culture. But the authors add one crucial detail:

> The remaining tissue was minced, plated on non-selective blood and chocolate agar, and cultured at 37°C under microaerophilic conditions as used for Campylobacter isolation. *At first plates were discarded after 2 days but when the first positive plate was noted after it had been left in the incubator for 6 days during the Easter holiday, cultures were done for 4 days*. (Marshall and Warren, 1312, italics added)

This detail on the time needed for culture to be successful had not been mentioned in Marshall's letter, which otherwise provides a similar description of the procedure. The lack of compliance of the bacteria to the attempts to "discipline" them through laboratory procedures, in fact, was overcome only after the "correct" amount of time needed for positive plates to appear was found out by accident, by someone leaving plates in the incubator over a period longer than that assumed to be needed for the bacteria to be cultured, on the basis of previous experience with other bacteria.[17]

In the "Results" section, negative results of attempts to grow spiral bacteria form the first 34 patients were negative, "probably because the cultures were discarded too soon" (Marshall and Warren, 1984: 1312). This incident seemed to provide further arguments for the already hinted at specificity of the bacteria as different from known species, on the basis of the time needed to culture them in the laboratory.

---

[17] For another account of this episode, see chapter 4.

The data produced through these different procedures were "coded independently in separate departments", and the findings were tested using appropriate statistical procedures for "positive correlation with the presence of either bacteria or gastritis".

The results were described in detail and documented with electron micrographs and tables, and a subsection was added on "Sources of Bias", including the characteristics of the sample population, the completion of reports and laboratory investigations, and how these problems were met.

The "Discussion" section, besides some explanations of methodological options, is remarkable, again, for its detailed engagement with a range of questions which had been previously formulated by both Warren and Marshall, and which were to become axial themes in subsequent research on the bacterium. These themes include the description and definition of what the bacteria are, how they are associated with a common gastric disease such as active chronic gastritis, how they survive and what is the causal path of bacterial infection.

Concerning the first question, Marshall and Warren restate their previous views on the nature of the bacterium: "a new species closely resembling campylobacters morphologically and in respect of atmospheric requirements and DNA base composition, but their flagellar morphology is not that of the genus *Campylobacter*" (Marshall and Warren, 1984: 1313). They thus propose to provisionally name the bacterium "pyloric campylobacter", which "will do to define the site where these organisms are commonly found and to indicate the similarity" to known *Campylobacter* species (Id.).

The question of the absence of an association between presumed or "known" causes of gastritis or of possible predisposing factors, such as the ones listed above, and the presence of histological gastritis, is corroborated by the study: none of the factors identified through the questionnaire showed evidence of "predispos[ing] to the infection. The authors offer a list of some of the "known causes" of gastritis and dispose of all of them, drawing on available literature: analgesic abuse, alcohol consumption, quantity of bile in the stomach (duodenogastric reflux), autoimmune disease or gastric ulcer. They conclude that "the aetiology of chronic gastritis remains uncertain" (Marshall and Warren, 1984: 1314).

The authors thus "undo" or weaken proposed associations between different types of possible causes of gastritis and histological gastritis. Although it is not possible to claim what the "cause" of gastritis is, they have succeeded, through their research design and assemblage of procedures, to put to the test a range of common explanations for gastritis, and show how they fail. As they admit, however, evidence of how chronic gastritis develops is still to be produced. Their positive contribution to this endeavour is to describe what they claim to be a "close association" between pyloric campylobacter and antral gastritis". Although a causal relation has not been demonstrated, the presence of bacteria when inflammation is present as well as their absence when there is no inflammation, which is true for the overwhelming majority of cases examined, suggest that the bacteria "are not commensals". This apparently modest statement is actually strengthened through further interpretation of the data: "The bacteria were not cultured unless the patient had histological evidence of both gastritis and pyloric campylobacter". And they confidently add:

> We know of no other disease state where, in the absence of complicating factors such as ulceration (…), bacteria and PMNs [polymorphonuclear lecucocytes] are so intimately related without the bacteria being pathogenic. (Marshall and Warren: 1984: 1314)

The question of the survival of "pyloric campylobacter" is a key issue for the claims advanced in the paper. Without a plausible explanation of how bacteria are able to survive in an inhospitable, acidic environment, Marshall's and Warren's claims are at risk of being gutted by critics bent on reasserting dominant views within the gastroenterology establishment. The authors dedicate a substantial part of the "Discussion" section to this topic. Their argument is summarized in the following terms:

> [P]yloric campylobacter grows in a near-neutral environment, in close contact with the mucosa and protected from the bactericidal gastric juice. The absence of these bacteria from past reports of gastric microbiology may be because only gastric juice was cultured (Marshall and Warren, 1984: 1314).

Once again, Marshall and Warren perform a double operation of providing a plausible explanation for an apparent anomaly which could jeopardize their claims and, at the same time, hint at a no less plausible explanation for the failure, by previous research, to come to terms with the problem. The suggestion seems to be that this failure is double: there is a failure to turn an anomaly into a problem requiring a fresh approach and this, in turn, leads to inappropriate method.

The final two paragraphs of that section offer a further insight into the (up to then unknown) aetiology of peptic ulceration. Discussing their findings of "[p]eptic ulcer as the only histological finding associated with histological gastritis and pyloric campylobacter, Marshall and Warren suggest that these findings are compatible with the hypothesis of a "bacterial aetiology, with continuing gastritis". Once again, they mention a piece of information which associates in a strong way with their hypothesis:

> Of ulcer-healing agents the only one thought to improve relapse rates is tripotassium dicitrato-bismuthate. This compound is bactericidal to pyloric campylobacter and in patients treated with it the gastritis improved and the bacteria disappeared. (Marshall and Warren, 1984: 1314)

This article thus set the stage for what was meant to be the demonstration of how bacterial infection was not just associated with, but was the cause of common gastric pathologies. There are four main achievements of the article. First, Marshall and Warren describe in detail the design and the results of a clinical investigation which provides what appears to be robust evidence, based on a sufficiently large number of cases to be of statistical significance, of an association between infection by the bacterium they provisionally call pyloric campylobacter and active chronic gastritis; secondly, they offer a systematic critique of prevailing views on the causes of both gastritis and peptic ulcer disease; thirdly, they suggest an alternative aetiology of both active chronic gastritis and peptic ulcer disease which is consistent with their data; and finally, they offer a plausible explanation for the survival of bacteria in the human gastric environment. As they notice in the last sentence of their paper, however, "cause-and-effect cannot be proved in a study of this kind". Another study, with a different design, would be needed to provide the final test of their belief that "pyloric campylobacter was aetiologically related to chronic antral gastritis and, probably, to peptic ulceration also". That study was to be reported on in a paper published in the following year by Marshall and his collaborators.

3.3.2. Fulfilling Koch's postulates: the 1985 article

The great challenge faced by Warren and Marshall in the mid-1980s was to take the next step after the observation that bacteria were found in the gastric mucosa of patients and showing that the bacteria could be isolated and cultured. That step consisted in the experimental demonstration of the causal link between bacterial infection and gastric pathologies.

The demonstration would be made at Perth Hospital, in Australia, and its account was to be published in The Medical Journal of Australia, on April 15, 1985. The article was co-authored by Marshall, the microbiologist David McGechie and John Armstrong, an expert in electron microscopy. It was an account of the attempt at the fulfillment of Koch's postulates as a way of producing proof of the causal relationship between infection by the observed bacteria and the pathologies the carriers of those bacteria had been diagnosed with. In the article, Koch's postulates are enunciated through the reproduction of a passage from a general, biographical history of medicine (Talbot, 1970: 763):

> *First postulate*:
>
> The organism, germ, should always be found microscopically in the bodies of animals having the disease and in that disease only; it should occur in such numbers, and be distributed in such a manner as to explain the lesions of the disease.
>
> *Second postulate*:
>
> The germ should be obtained from the diseased animal and grown outside the body.
>
> *Third postulate*:
>
> The innoculation of these germs, in pure cultures, freed by successive transplantations from the smallest particle of matter taken from the original animal, should produce the same disease in a susceptible animal.
>
> *Fourth postulate*:
>
> The germs should be found in the diseased areas so produced in the animal.[18]

Koch's postulates constitute a set of statements postulating the demonstration of strong associations between certain elements and entities and, at the same time, they establish the conditions under which that demonstration is regarded as successful. As we shall see, they provide a strong rhetorical resource which allows the simultaneous demonstration of the existence of the associations claimed by Marshall and his co-authors and the inscription of that demonstration in the history of research on the links between specific micro-organisms and specific pathologies.

In the introductory section of the article, the authors claim that the association between the bacterium they call *Pyloric campilobacter* – a bacterium recently identified and described – and gastritis has been confirmed in studies performed on patients in several countries.

[18] From here on, numbers in brackets without further indications refer to page numbers of the 1985 article.

Nevertheless, they add, "the possibility remains that these bacteria are not the primary cause of gastritis, but are merely opportunistic commensals of previously abnormal mucosa" (436).

Thus the need to fulfil Koch's postulates for these bacteria. The first and second postulate had already been satisfied through previous work, whose results were available in the publications discussed earlier. The authors recall Koch's postulates and summarize the results of previous work. The fulfilment of the first postulate –

> "The organism, germ, should always be found microscopically in the bodies of animals having the disease and in that disease only; it should occur in such numbers, and be distributed in such a manner as to explain the lesions of the disease"

is accounted for in the following way:

> The disease in this case is an inflammatory condition of gastric mucus- secreting epithelium at present variously termed 'type B gastritis', 'antral gastritis', 'active chronic gastritis', 'superficial gastritis', and 'acute gastroduodenitis' (…). In this disorder, P[yloric] C[ampilobacter] is almost always present, adherent to the gastric mucosa. The bacteria do not attach to cells of intestinal type, so they are not found in the duodenal cap, except on islands of gastric epithelium (…). Such 'metaplastic' gastric epithelium can be found on the borders of duodenal ulcers, and in the duodenal cap of patients with duodenitis (refs. 8-10) (436).

As for the second postulate – "The germ should be obtained from the diseased animal and grown outside the body" –, the authors notice that the bacterium had been isolated from a patient diagnosed with gastritis in 1982, and add:

> Since January 1983 PC has been cultured from over 150 patients in our hospital. In almost all patients, an infiltration of polymorphonuclear cells has been found in the specimens of antral mucosa on the initial or a subsequent biopsy. (436)

The aim of the authors in the 1985 paper is thus to move on to the description and discussion of the experimental procedure through which they allegedly fulfilled the third and fourth postulates: the ability of the bacterium to colonize the tissues of the normal gastric mucosa and to induce gastritis (436).

The form and content of the introductory section of the article appear as a sort of fusion of the sections Medawar names "Introduction" and "Previous Work" – what would nowadays be called "State of the Art". But in this case that section is far more important than Medawar's criticism suggested. In fact, it performs several different operations. First, it situates the work accounted for in relation to previous work and, in particular, to the work establishing the conditions under which the scientific and clinical relevance of what is accounted for is to be assessed. This previous work, in turn, has been carried out and published, to a large extent, by the principal author and thus allows the latter to appear as a major contributor to an alleged continuity with well-established research and experimental traditions within bacteriology (as is clear from the central role of the reference to and commentary on Koch's postulates as a major feature of the textual economy of the article).

But the reference to previous work is a resource as well for a never explicitly assumed but nonetheless recognizable break with "official" knowledge on the cause of common gastric pathologies. The modest reference to a bacterium which has been recently described and to a set of studies which seem to rest upon a likewise modest accumulation of observations allows the "anchoring" of the article and of the work underpinning it in the collective effort and the

cumulative result of the labour of a community of researchers. References to published work create a citation environment which is itself performative of a "core set" (Collins, 1992) of researchers, pathologists and clinicians. The introductory section is thus an early moment in the double narrative reconstruction of knowledge on gastric pathologies and bacteriology: a reconstruction of the history of research on the causes of common gastric pathologies and a reconstruction of the web of researchers, resources, patients and biomedical entities giving shape to a new actor-network (Latour, 1987, 1999).[19]

Self-experimentation and its textual inscription

The next section deviates as well form the traditional form of the article discussed by Medawar. There is a brief mention of the "histological and microbiological techniques" used as being identical with those described in another article in the same issue of the journal. The only specification has to do with the method for the fixation and staining of specimens for electronic microscopy (436). The section is mostly focused on the presentation of the third and fourth of Koch's postulates and on the procedures followed for their fulfillment. Once again, the third postulate is quoted:

> The innoculation of these germs, in pure cultures, freed by successive transplantations from the smallest particle of matter taken from the original animal, should produce the same disease in a susceptible animal.

It is as part of the procedures aimed at the fulfilment of this postulate that an episode is to be found which would become a major asset for the rhetorical power of the article and, subsequently, would have great salience in the history of the bacterium which was to become *Helicobacter pylori*.

The reader is told that the subject of the experimental procedure for the fulfilment of Koch's third postulate is "one of the writers (BJM), a 32 year-old man, a light smoker and social drinker, who had no known gastrointestinal disease or family history of peptic ulceration" (436). Marshall himself will thus submit to an endoscopical examination and to biopsies of several parts of the stomach. These, as shown by the illustrations included in the article, reveal no "inflammation or ultrastructural anomaly". No signs of the bacterium were found either in swabs of gastric mucus, nor was it possible to culture the organism from biopsies, "despite the successful isolation of PC from two patients with duodenal ulcers and one patient with gastritis in the same gastroscopy session" (436). This patient will provide the bacteria to be cultured for the experiment. Before the experiment, two mice were inoculated with the bacterial culture but showed no identifiable effects. It was established as well that the cultured material was sensitive to five different antibiotics – just to make sure that the effects of self-innoculation would be reversible… The isolate was freeze-dried and later "revived" for the experiment. One month later,

> when electron microscopic results were available and any lesion which resulted from the initial biopsies could be presumed to have healed, the subject fasted overnight and received premedication with cimetidine (600mg) at 8 a.m. to produce temporary achlorhydria. At 11 a.m., the subject swallowed the growth from a flourishing three-day culture of the isolate (about 10 to ninth power colony-forming units) which was

[19] For another account, see Chapter 4.

> suspended in 10 ml of alkaline peptone water (pH 8.0). He took no food for two more hours, after which he ate normal food. No medication nor alcohol was taken during the subsequent fortnight (436).

The description continues with an account of the "increased abdominal peristalsis" (parenthetically described as "audible gurgling at night"), noticed by the subject in the 24 hours subsequent to the ingestion of the bacterial suspension. Over the next week, no additional symptoms appeared, but on the seventh day after ingestion the subject "woke early and vomited a little mucus at 6 a.m. No pH recording was taken, but the subject was surprised that the vomitus did not have an acidic taste. He had no fever, but had a headache on four occasions during the second week. His faeces softened slightly, but it did not progress to diarrhoea. The subject was irritable, and appeared ill during the second week of the experiment; several colleagues observed that he developed 'putrid' breath." (436-7). On the 10th day, the gastroscopy was repeated, with the aim of checking whether there was infection. But unlike what had happened during the first gastroscopy,

> the subject tolerated it poorly with much heaving and regurgitation of mucus, which made it necessary to obtain biopsy specimens quickly and terminate the procedure. The gastric mucosa appeared normal, but the endoscopist stated that it was `soft´, that is, the biopsy tissue could be pulled away very easily, compared to the initial biopsies. The subject did not feel a `tug´ when the biopsy specimens were taken, as he did at the initial and subsequent endoscopies. Two samples were taken from the antrum, one for histological examination and one for culture.

A description follows of the samples and of the results of histological analysis: the specimen was "small and fragmenting", but contained "many polymorphonuclear neutrophil leucocytes (PMNs)" in the lamina propria and on the surface of the mucosa, as could be readily seen on one of the illustrations of the text (Figure 2 A). Another figure (2B) shows evidence of anomalies in the epithelial cells, as well as the nearly total absence of intracellular established through an appropriate staining procedure (periodic acid-Schiff (PAS) staining). Spiral bacilli were visible in a third figure (2C), adhering to the epithelium (surface and glandular) and "among PMNs in the mucus" (437). Finally, and through the reprocessing of paraffin-fixed tissue, it was possible to confirm the presence of bacteria through electronic microscopy (Figure 2D) (437).

This rather lengthy rendering of the technical descriptions is intended to display the way the article inscribes the chain of operations and the web of associations necessary to successfully perform the (self) experiment through which Koch's third postulate was to be fulfilled. A human subject, different pieces of equipment, procedures performed by lab technicians, electron microscopists and bacteriologists, a subject providing the microorganism for culture, the microorganism itself, and its compliance to the action it is expected to take: this provisional assemblage of heterogeneous elements and processes is brought together into an account which makes available to "virtual witnesses" – in this case peers – the successful performance of the experiment.

This technical digression is briefly interrupted to add further description of subject's experience – "The subject continued to feel hungry on wakening, early in the morning, but no new symptoms developed and no more vomiting occurred" – and resumed, describing additional procedures and their outcomes:

> Gastroscopy was repeated on the fourteenth day, when biopsy specimens for light and electron microscopy were taken. It was expected that continuing gastritis and PC infection would be present, but no organisms could be seen in any of the specimens. At this time, the histological changes had diminished. PMNs were once more absent, and only a minimal accumulation of mononuclear cells had remained [as could be seen in Figure 3A].

The mucus content of epithelial cells prepared with PAS staining had increased, but was still below values considered as normal. Figures included in the text (437, Figures 3B, 3C) were presented as visual evidence both of the still abnormal mucus content and of ultrastructural changes associated with colonization by PC. References to the subject appear again, but this time, rather than drawing on an account of his experience, a step back is taken and a more "distanced" description is offered. On the 14th day, the subject initiated therapy for infection, which consisted of the administration, twice a day and for the period of a week, of 500mg of tinizadole – recall that before Marshall self-administered the suspension containing the bacterium, the sensitivity of the latter to tinizadole had been tested and confirmed. The symptoms of infection disappeared within 24 hours after the therapy was initiated. A test using passive hemoagglutination showed that the production of antibodies to PC had been discontinued. Notice that no more references are made to the feelings and sensations of the subject. The phenomenological mood of previous passages has faded away and given room to a more conventional, objectivist way of accounting. A feeling like relief and the accompanying bodily sensations are left out of this account.

The authors move on to claim that the fourth of Koch's postulates has been satisfied:

> A Gram-stained specimen of the biopsy taken on the tenth day showed the presence of spiral bacteria, and these were cultured after 48 hours. The organism was identified as pyloric campilobacter by the methods previously described. Antibiotic sensitivities were the same as in the inoculating strain. The isolate has been freeze-dried, and is available from the writers on request (437).

The process has thus come full circle. The claims made by Marshall and Warren in previous publications are reformulated as the fulfilment of Koch's first two postulates, and the third and fourth are satisfied through a combination of an unorthodox – though not unprecedented – use of self-experimentation by the principal author and an assemblage of technical procedures which allow strong associations between the symptoms described by the experimenter, the observations made through the mobilization of a range of clinical and laboratory procedures and the bringing together of these processes as a text which both asserts the novelty of the results and their reliability as confirmed through the time-honoured approach subsumed under Koch's postulates. A range of easily recognizable – for both specialists and non-specialists, although through the mobilization of different expectations and conventions of reading and interpretation – "external signs" of matter-of-factness is offered, including the detailed rendering of the list of clinical and laboratory procedures deployed by the authors, the inclusion of figures which provide visual evidence of the author's claims at different stages of the demonstration they intend to make, and, of course, a sort of phenomenological description of the experience of being infected and of how the infection sets in, as it is translated into bodily sensations and reactions. All these elements support each other and call on readers to acknowledge the strength of the associations between the observed and cultured bacterium, infection of the stomach, symptoms of gastritis and effective therapy. In short, Marshall and his co-authors have rehearsed the heroic tale of the late 19th and early 20th Century pioneers of microbiology who established what came to be regarded, before the

advent of molecular approaches, as the scientific explanation of disease, of its causes, and of how these could be known and acted upon through appropriate therapies. There is, thus, a tension in the way Marshall and his co-authors call upon the reader to accept their claims: they are a breakthrough, a blow to established views, but they are also a demonstration of the power of "old", pioneering approaches to biomedicine. The latter, in fact, appears as a condition for the validation and subsequent destiny, as a fact established through appropriate scientific procedures, of the former (Latour, 1987; Latour and Woolgar, 1986). There is here, of course, food for thought for the scrutiny of claims of the process leading to the "discovery" of Helicobacter pylori as an episode in the history of science akin to a Kuhnian revolution.[20]

In the "Discussion", section, the authors do not mention how the subject experienced infection, going through gastroscopy, treatment and recovery, but only the conclusions of the process of identifying and describing the infection and its eradication. They do add, however, a bibliographical reference which is a major resource for the narrative reconstruction of the production of knowledge of the origins of gastric pathologies, and which, once again, stresses the importance of symptoms as they are experienced by subjects (Osler and MacRae, 1920).

The self-experiment performed by Marshall is one of the best-known episodes in the demonstration of the causal links between bacterial infection and common gastric pathologies.[21] It should not be forgotten that all experimentation involving human subjects which may be potentially dangerous to the health or well-being of those involved, or even threaten their lives, always generate ethical problems. Instances of self-experimentation are likely to generate even more controversy. Interestingly, this question is never mentioned in the article. The authors are clear about the role Marshall played as subject of the experiment and the procedures and precautions taken to reduce risks associated with the experiment without compromising its credibility are carefully described. In fact, the description included in the article does more than specifying procedures in order to make them available to readers – in other words, it is not just a way of affording the "virtual witnessing" of the experiment, but it should be understood, at the same time, as a way of safeguarding the credibility of the procedure and the safety of the subject involved in that procedure. The description of precautions may be understood as constitutive of the fulfilment of Koch's postulates as well as an account of the way the subject was protected.Thagard's critical remarks on sociological or science studies approaches to science miss the whole point of this kind of approach: the reconstruction of the "messy" and contingent process of generating new knowledge and objects that "matter" in the double sense of the word, as Barad uses the term (see the discussion in Chapter 6, infra).

---

[20] See, in particular, Paul Thagard's account of this episode. Thagard is interested in testing his theory of scientific innovation, and thus uses the case of Helicobacter pylori not as a story characterized by the heterogeneity of its protagonists and the contingency of its dynamics, but as an illustration of a full-fledged theory which owes a lot to Kuhn's work.

[21] Another episode of self-experimentation occurred in New Zealand. Its main protagonist was Arthur Morris, and an account of the research it was a part of was published in 1987 by Morris and Nicholson. Unlike Marshall, Morris would suffer from long-term effects of the experiment.

3.3. Discussion

Adding a section called "discussion" may seem a concession to a stylistic feature of scientific articles Medawar strongly objected to. But it certainly has the virtue of allowing a final comment on the approach we have presented to be added without the rather strong commitments suggested by a title like "Conclusions". We thus move now, to close this chapter, to a summing up of the main arguments unfolded in previous sections.

The narrative by Marshall (as the main author of the article which provided the main source for this chapter), displays, first, his double condition of author and subject of the experiment on which the author reports. This allows him (and his co-authors) to draw on what appear to be two distinctive repertoires of scientists' discourse: an "empiricist" (Gilbert and Mulkay, 1984) and an "experiential" repertoire. This may well be an appropriate way to describe the features of scientific discourse as they are found in this particular text, following an approach which has successfully made its way, thanks to the work of authors like Gilbert and Mulkay, as one of the key approaches in the analysis of scientific discourse. A close reading of the text, though, suggests that, beyond the identification, in the text, of the deployment of these two repertoires, we are dealing here with an explicit attempt at "translating" the descriptions the subject produces of his experience into a vocabulary and style consistent with the conventions of the scientific article, namely the suspension or elimination of explicit references to human subjects and actions. The account of the experience of the subject is thus transformed into an input to the text based on self-observation which is expected to share the main features of descriptions, in the biomedical literature, of symptoms based on clinical observation or on the conversion into the clinical vocabulary of accounts of those symptoms by patients. If, at times, two voices seem to coexist in the text, they are subsumed under a discourse which reconciles them, in terms which are those set by biomedical discourse and its conventions, through the articulation - in the double sense of making textually explicit and of bringing together elements which were not necessarily related – of clinical (self)description and the account of laboratory procedures.

The scientific authority which is an effect of the text is an outcome of its capacity to relate and to create strong associations between the description of the symptoms, the results of different types of clinical practices and laboratory procedures and the references to existing literature, thus achieving what we have called, drawing on Rouse's work (Rouse, 1996), a double narrative reconstruction: of the specific research being accounted for and of the field it relates to, which is transformed by that research and whose "official" and unofficial histories are thus reconstructed.

The reference to Koch's postulates and the (successful, by the authors' standards, and as thus acknowledged by a considerable fraction of their peers) attempt at their fulfilment turned up to be a key element of the narrative reconstruction performed by the text. Attachment of the article to previous work by Marshall and his collaborators allows their contributions to be assessed as central to that reconstruction. The mention of a text by Osler and MacRae, published in the 1920s, which includes a description of symptoms very similar to that of the self-experiment by Marshall, is an additional resource for reassessing the importance of a detailed description of symptoms as a way of providing proof that previously observed conditions may be explained in a robust way as the outcome of bacterial infection. But it provides as well a plausible attachment to the body of knowledge of gastroenterology and a reinterpretation of a range of clinical and laboratory observations which had been explained

away on the basis of established wisdom within the specialty. The description of the self-experiment thus performs a role which, rather than compromising the postulate of objectifying distance, actually opens the way to the latter and confirms its necessity, by showing that observations – including self-observation – by themselves are not enough to establish the truth or matter-of-factness of a statement. A further step is needed, that of producing evidence of infection and of its cause under controlled conditions, of which self-experimentation is a part. It is the extraction and processing of biological materials and the interpretation of the outcomes of these procedures and of the objects they generate – what Rheinberger (1997) calls epistemic objects, objects which can be put to the test of their matter-of-factness or artifactuality – that allows the description of symptoms to be endowed with meaning form a biomedical standpoint. Under these conditions, bringing the author (back?) into the text does not amount to an explicit introduction of a more reflexive approach to the conditions under which both the research and its accounts are produced – or mutually produced, as ethnomethodologists have taught us (Lynch, 1993) – or of the relationship between the researcher as an embodied entity and the "body of knowledge" he/she is a contributor to (Lawrence and Shapin, 1992).

Its purpose seems rather to answer the need for a kind of evidence which is impossible to produce through other means and other subjects, such as patients (for ethical and legal reasons). Self-experimentation appears, under these conditions, as a viable option for generating that kind of evidence without the ethical and legal restrictions attached, more generally, to experimentation with human beings. The operations of inscription performed by the authors thus allow the objectification of the experience of disease in a way which contributes to the reconstruction of both experimental and observational procedures and of the history of gastroenterology and bacteriology.

4. Chronicles

This chapter offers an account of the early biography of the entity which came to be called *Helicobacter pylori* (Hp). It is intended to be neither a metanarrative of the process through which Hp became an established, bona fide biomedical entity, nor what Woolgar (1976) called a "working account" of that process. It may, of course, be read as either of these. But its purpose is far more modest and limited. It is a narrative constructed out of sequences and fragments of other narratives – namely first hand accounts of participants and accounts in the form of scientific articles and other forms of publication - and it is framed within a specific approach, namely a version of Actor-Network Theory (ANT).[22] Its purpose is to provide a reconstruction of the paths through which a range of heterogeneous human, non-human and technological actors/actants coalesced into a particular configuration of knowledge, laboratory and clinical practices and biomedical entities, giving rise to *Helicobacter pylori* as an "obligatory passage point" (Latour, 1988) in gastroenterology. This chapter has as its main source two first-person accounts by J. Robin Warren and Barry Marshall which display some of the features of a *chronicle*:

> Chronicles do represent historical events in a narrative form, but that appears to us as an unfinished story. It seems to us that the chronicle "aspires to narrativity", as [Hayden] White nicely puts it, but does not succeed in achieving it. Chronicles simply terminate, without providing a defined closure. The chronicler remains in his own present, leaving things unresolved, if by unresolved one means lacking a narrative resolution in a story form structured by a beginning, middle and end. Hence, while both chronicles and annals do contain a type of chronology as their principle of organization, they lack closure. (Rabinow, 2003: 78)[23]

The accounts by Warren and Marshall will be treated here as chronicles in the sense Rabinow suggests: a text which is organized in a chronological sequence, reporting on events witnessed or experienced by the author and which does not entirely achieve the closure expected of a narrative. Although the texts may well be read as more conventional first-person narratives, a close reading of them and, in particular, a consideration of their relation to the overall textual economy of the collection it is part of (Marshall, 2002) underlines the sense of their lack of closure, both as part of the collection and from the point of view of the narrative economy of the particular accounts. As the texts were published (and presumably written) two decades after the events they report on, their "reconstructive" nature is made apparent, above all, by some retrospective thoughts shared by the authors. Interestingly, though, these actually contribute to highlight the open-endedness of the account. There is a discontinuity between the processes reported on and some of the future events these interpolated thoughts hint at. How did the story go from the "here and now" of the reported processes to a future which had to look astoninglishly different to those who were the main characters of those processes? Other contributions to the collection do try to fill in the gap, but this adds to the "chronicle-like" lack of closure of the stories told by Warren and Marshall.

---

[22] For presentations and discussions of the heterogeneous domain of ANT, see, among other, Law and Hassard (1999), and Latour (2005). We have drawn mostly on the version presented by Callon (1999). Our use of the accounts by Warren and Marshall has been heavily influenced by Latour's use of Pasteur's published writings (Latour, 1988).

[23] On the chronicle as a genre and on its use in science studies and, more broadly in studies of what he calls "the contemporary", see Rabinow (2003: 76-90, especially 77-79).

Let us now take a brief look first at some of the "internal" features of these two texts. Their central character is a bacterium, which takes on a variety of modes of existence - as a puzzle for clinicians, as an "impossible" entity, as a bacterium appearing in biopsies, as a strain of a known species of bacterium, as an infectious agent, as a new species of bacterium, as an entity in pathology, clinical practice and microbiology and, for the "second-order observers" who produce an account based on these two accounts, as a biomedical object characterized, depending on how it is approached, by its salience, emergence, productivity or embeddedness (Daston, 2000)…[24] But the bacterium is of interest to us in so far as it becomes attached or un-attached to a range of other actors/actants which are inseparable from the qualities it displays under each of its modes of existence. What makes Warren's and Marshall's texts unique documents on the making of H.p. as a biomedical entity and as a pathogen is the astonishing amount of detail they supply on time, place, actors (human and non-human) and events and the way these are brought together in a chronological account of a trajectory which remains open-ended, and thus open to diverse and contested interpretations.[25]

A second feature of these texts, which was already briefly mentioned, is that they should be read as a key part of an unusual editorial initiative. In 2002, Marshall published an edited volume entitled *Helicobacter Pioneers: Firsthand Accounts from the Scientists who Discovered Helicobacters, 1892-1982*. The book included 16 chapters, plus a foreword by Yale School of Medicine Professor Irvin M. Modlin, and a preface by Marshall. The subtitle, in fact, falls short of an accurate description of the contents of the book. Although all contributors are scientists who, in different ways, have been involved in research which involved or stumbled on bacteria found in the stomach of mammals – including humans –, not all the contributions are "firsthand accounts". Some are broader, though focused, historical accounts of early observations or experiments or biographical notes on those who made those observations or experiments. Others consist of retrospective accounts of episodes associated with some of these observations, and indeed based on firsthand involvement with them. Others still focus on recent developments in diagnosis and therapies of common gastric pathologies. A fourth type of contribution, represented by the chapters by Robin Warren (ch. 14) and Barry Marshall (ch. 15), is closer to what we have proposed to call a chronicle of the process(es) leading to the observation of bacteria in biopsies of human stomach samples and the subsequent demonstration of their association with gastric disease. Both chapters refer to a "discovery" – of a bacterium in Warren's account, of the same bacterium as the cause of peptic ulcer disease in Marshall's chapter. Surprisingly, and in spite of the claim by Warren and Marshall of having discovered H.p., several other chapters have titles making similar claims and at earlier dates (chs. 10 and 11). Since, as Stengers and Bensaude-Vincent (2003: 103-107) have recently reminded us, the point of claiming a discovery is recognition, early discovery should invalidate later claims, like those made by Marshall and Warren. The whole volume, however, seems to be organised as a kind of genealogy of the discovery by the two Australians. Apparently, such an exercise would undermine their claims. But the whole tone

[24] For thoughtful commentaries on second-order observations, see Rabinow and Dan-Cohen (2005), and Rabinow (2008). On Daston's four approaches, see Chapter 2.

[25] For a graphic representation of the associations enacted by Warren and Marshall, which can be followed in their respective accounts, see the Appendix to this Chapter.

and direction of the contributions, in fact, does not challenge, rather reinforces the recognition of these claims.

The Preface and Foreword provide two different directions as to how to read the book and the contributions to it. Marshall's Preface states that the book "is not meant to be a textbook, but rather provides background and the human touch to a discovery process that took almost a century" (Marshall, 2002a: xi). There is thus a sense the editor seeks to share of a collective endeavour which he (and Warren) successfully brought to an end, that of discovering *Helicobacter pylori*. The "pioneers" referred to in the title are all those who, at one point or another, observed or reported on spiral-shaped bacteria in the stomach of humans or proposed some link between bacteria and gastric disease. Since the late 1980s, Marshall had been trying to locate these "pioneers" and, when they were still alive, get first-hand accounts on their observations. He comments that "[a]s the chapters arrived I was pleased to see that many were written by colleagues who had actually taken part in the studies, or who had first-hand knowledge of the pioneer." (Id.). Marshall then adds a sentence which may be read as a general instruction, an epistemological and sociological key to the reading the collection and the individual contributions: "Some of the accounts literally brought tears to my eyes as I recognized a familiar pattern of medical conservatism, lack of resources, or merely making an important discovery in the wrong place at the wrong time" (Id.). In other words, to be acknowledged as such, a discovery has to be made in the right place and at the right time which, in this case, were Australia in the late 1970s-early 1980s…

The Foreword, by Yale Professor Irvin Modlin, describes the book as "the crowning achievement of a lifetime's work by Barry Marshall". The story told in the contributions to the book is

> little less than a modern-day odyssey. The trials and tribulations of those who sailed the stormy waters of H. pylori research in the last century are beautifully detailed, with the sometime tragedy, heartbreak and even grandeur of their observations. The hurdles of fate, the petty animosities, the entrenched dogma of medical society and the prevailing winds of understanding all buffeted the lives of those who dedicated themselves to the elucidation of gastric mucosal pathobiology. We learn that for many the journey itself was the pleasure and the destination a secondary consideration, but for others it was clearly much like the road to Thebes and their outcome no different to that of Beckett's `Waiting for Godot´. Yet such is the chronicle of human experience and it is the duty of those who have undertaken such trials (prospective or retrospective) to record them so that others may learn from their experiences. (Modlin, 2002: ix)

Helicobacter Pioneers is thus read by Modlin as both a modern epic and an edifying record of the trials of scientific discovery.[26]

Despite the differences in size, style and generic conventions, the contributors to the volume seem to be moved by two main concerns. The first is to document early observations of bacteria in the stomach and other episodes which, in different ways, seem to anticipate Warren and Marshall's achievements. The second is to explain why these early episodes fall short of these achievements, and thus are not "true" discoveries. Explanations for this failure are mainly of two sorts: epistemological – linked to failures to live up to standards of good scientific practice, adopting a wrong or inadequate conceptual and observational frame or simply resisting the recognition of solid empirical evidence – and practical/sociological, linked to limitations of materials and instruments or, in a more implicit manner, as Marshall

[26] The epic key actually dominates the text.

states it, "making an important discovery in the wrong place at the wrong time" (Marshall, 2002: xi). One chapter briefly hints at the discovery of H.p. as having a collective and geographically-focused character (in the Pacific), although this fits uneasily into a book which is filled with descriptions of geographically scattered, early 26 The epic key actually dominates the text observations and experiments. Throughout most of the accounts, *Helicobacter pylori* seems to lurk behind all the different, mistakenly named or classified entities or beneath the procedures intended to make it visible and display its attributes for the benefit of researchers and clinicians. Interestingly, although the volume as a whole and the different contributions enact the difficulties of using the concept of "discovery", there is no specific discussion of it. A final, striking feature of the accounts is the absence of some of the now usual characters in stories of biomedicine, such as molecular genetic approaches or cutting-edge technologies. We are rather invited to guide visits to a world which seems to reappropriate the tools and approaches of "heroic", late 19th Century medicine, at the time when the key to the understanding of disease seemed to lie in the understanding of infection and infectious agents. Pasteur and Koch, rather than Watson and Crick, are lurking in the background.

A close reading of the contributions, however, suggests that there is more to these stories. First, the detailed accounts, by Warren and Marshall, of the work of "discovery" suggests that the ontological status of the entities observed and, later, their stabilization as entities of a given species were, in fact, at stake in most of the episodes. Rather than epistemological failure, it may be argued that what the accounts display is the active work of constituting ontologically unstable entities into scientific facts, or, as Ludwik Fleck (1979/1935) would describe it, the genesis and development of bacteria in the stomach as scientific facts. Secondly, the accounts, rather than focusing on the "pioneers", appear to describe the way instruments, clinicians, pathologists, microbiologists, patients and biological entities are associated through specific practices to produce a particular type of entity which came to be called *Helicobacter pylori*. This holds in part for some of the other contributions. In other words, the stories can be read as biographies of *Helicobacters*, biography being understood, here, in the terms proposed by Daston (2000: 14), as addressing scientific objects as both real and historical, as being characterized by an "ontology in motion", as inviting us to blur the distinction between invention and discovery, as being the outcome of specific, historically situated encounters between scientists and the world. Warren's and Marshall's chronicles of the making of *Helicobacter pylori* are unusual sources for this engagement with the "ontology in motion" of scientific objects or entities.

4.1. The approach

As mentioned above, the approach taken in this chapter is based on Actor-Network Theory. We have drawn on one of the early versions of the approach (Callon, 1999/1986). Rather than a theory, ANT is a set of more or less tightly-connected approaches, sharing a number of common ontological and procedural premises.[27] We shall leave aside the many arguments and discussions which have turned ANT into a lively filed of disputes and a repertoire of robust tools for analysing scientific activity, socio-technical dynamics and controversies. The version

[27] See note 23, supra.

we are drawing upon here is particularly suited to the task of tracing the making of strong associations of human and non-human actors. The history of the making of H.p. as a biomedical entity is an exemplary instance of the kind of process Callon and Latour have described and discussed in their pathbreaking work of the mid-1980s (Latour, 1988; Callon, 1999/1986). We shall not dwell here into the debates over the symmetrical approach to human and non-human agents/actants. Treating *Helicobacter pylori* (or the bacteria that pre-exist it) as an actor is a heuristic move which, as we hope to demonstrate, allows its key role in the narrative we offer to be highlighted.

Callon (1999/1986) distinguishes four moments in the process of creating strong associations through what is called in ANT "translation": problematization, interessment, enrolment and mobilization. In fact, as Callon points out, these four moments tend to overlap, and any account of the process of translation will have to come to terms with the "messy" or contingent ways of which translation is made. In this case, it is possible to identify two key actors, Robin Warren and Barry Marshall, as the "primum movens of the story" (Callon, 1999:68). As is common practice with ANT approaches, we shall organize our account around the following of these two actors. In other words, our option is to observe observers as they observe/enact a new entity.

The first phase, *problematization*, corresponds to the process through which given actors become indispensable to respond to a given situation. It includes defining the problem in a way which compels other actors to join those who problematize. In this case, as we shall see, those who problematize are not just Marshall and Warren, but the bacteria as well: the latter literally set up a problematic situation which Marshall and Warren will respond to through further problematization. Alternative problematizations are still possible, so further steps are needed for one of them to assert itself as the "right" or the "only" way to address the situation. Problematization involves the definition of an obligatory passage point which other actors have to go through in order to adequately and successfully (according to their expectations or aims) address the situation. The second phase, *interessment*, requires allies who have joined the particular definition of the problem advanced in the first phase to be "locked into place", and to make the costs of not allying themselves with the "problematizers" a costly move. This is achieved mainly through "interessment devices", which are placed between the prospective allies and other, opposing or potentially hostile actors. The next phase, *enrolment*, involves the assignment of specific roles to all parties which have been "interested" and their coordination. This is achieved, in situations like the one we are dealing with here, through, among others, the production of statements claiming more certainty and the means to put them to tests which will either confirm their capacity to resist criticism or alternative problematizations or, alternatively, display their vulnerability. Finally, the fourth moment, *mobilization*, refers to the way in which "problematizers" become spokespersons for the other actors who have been "interested" and "enrolled". The process we will be following corresponds to the early stages of the making of the entity later called H.p., i.e., until the successful demonstration of its causal links with common gastric diseases. We have avoided organizing the account into distinctive sections corresponding to the four moments or phases mentioned above. Again, these do not appear in chronological sequence, but are entangled in different ways at different stages of the account. They should be regarded as "sensitizing devices" for helping with the identification of significant elements in the story, rather than as a set of constraints on what and when should be reported on.

Before moving on to our "second-order" account of Warren's and Marshall's first-hand accounts, we offer in the next section an introduction to the background to those accounts, reconstructed from the contributions to *Helicobacter Pioneers* and complemented by other sources.

4.2. Helicobacter before Helicobacter, or the impossible infection

In the late 19th Century, there was little agreement within the medical profession on the causes of common diseases of the gastric tract, such as gastritis or peptic ulcers. The possibility of these pathologies being caused by some type of infection was discussed, and some pathologists, in several countries, reported observation of bacteria in the stomach of mammals of different species. In 1875, Botchett and Letulle identified bacteria in the margin of ulcers. A few years later, in 1881, Klebs "noted the presence of bacilli-like organisms in the lumen of gastric glands, with corresponding inflammatory cell infiltration of the gastric mucosa (Fukuda *et al.*, 2002: 19). Other observations and experiments followed such as those by Letulle who, in 1888, demonstrated that Staphylococcus aureus induced acute gastritis in guinea pigs; the following year, Jaworski observed the presence of Vibrio rugula in the stomach. The Italian physiologist Giulio Bizzozero, in turn, described the colonization of the stomach of dogs by bacteria, reporting in 1893 that "spirochete organisms were present in both the pyloric and fundic mucosa and were distributed from the base of the gastric glands to the surface of the epithelial cells" (Fukuda *et al.*, 2002: 19). Bizzozero was renowned for his "rare power of observation (considering the limited technology)", his ability in histological techniques and his devotion to the new discipline of "pathological physiology" (or simply "biology", as Rudolf Virchow christened it). It is the convergence of these three features, plus Bizzozero's specific interest in studying the stomach, that made possible his observation of bacteria in the stomach of dogs (Figura and Bianciardi, 2002: 6). Salomon (1896) described the transmission of gastric spirochetes; Krienitz found spirochetes in the gastric content of a patient with gastric cancer… The list of those who observed and reported on the presence of bacteria in the stomach of mammals, including humans, but also of those which induced gastric disease in animals through infection by bacteria is long, and leads us all the way to the early 1950s. It should be noticed that

> the fact that the frequency of these spirochete organisms in humans was lower than in other animals and also that these researchers could not transmit the organisms to show an etiopathologic role precluded them from concluding that the spiral bacteria were actually related to human gastric diseases (Fukuda *et al.*, 2002: 19).

Bacteria were there, in the stomach of mammals, including humans; disease was there as well, and could in some cases be plausibly associated with the presence of bacteria; the instruments and skills were available to allow the observation of these micro-organisms and of diseased organs; but researchers, pathologists and clinicians were not interested, inclined, or just failed, to "discipline" both bacteria and human and non-human organs and patients to provide proof of an association between these bacteria and disease through infection. Bacterial infection as a cause of common gastric diseases thus did not become a biomedical fact.

In 1954, Ed Palmer, an American gastroenterologist, performed an analysis of 1140 specimens from patients, with the sated aim of determining the presence of the spirochete organism described earlier by, among others, Doenges (in 1938) and Freedberg and Barron

(in 1940), both cited in the paper Palmer published that same year. Palmer used a state-of-the-art vacuum tube technique for the endoscopies through which he obtained the specimens. His conclusion was that histological analysis did not provide evidence of the existence of spirochete or spirochete-like organisms in his specimens. He thus went on to claim that there were no bacteria to be found in the human stomach, and that earlier reports of observations of these organisms were in fact due to contamination, namely through post-mortem colonization of specimens, organisms from the oral cavity or putrid ulcerations. Spirochete organisms would normally enter the body, he claimed, through the mouth and thus get to the gastric juice (Palmer, 1954). Palmer's paper was the cornerstone of the "dogma that bacteria could not live in the human stomach" (Fukuda, 2002: 20), which persisted for the next three decades.

Palmer's study appeared as a successful example of recruiting a range of heterogeneous actors and resources to produce the non-existence of "spirochetes in the stomach". He had patients (no less than 1000, yielding 1140 samples, since a number of them went through two gastroscopies) providing specimens; he had state-of-the-art techniques at his disposal; and he had a coherent explanation for the reported absence of spirochetes from the organism. His position within the specialty endowed his work with an authority which could not be matched by the cautious statements of the authors who he claimed were wrong.

Palmer's article thus became the orthodox view in gastroenterology on the status of the claim of bacterial infection to be the cause of gastric disease. Professors and students of medicine and clinicians all over the world were socialized into a view which discarded the possibility of there being any value in that claim. The cause of common gastric diseases thus came to be attributed to excess acidity, and treatment based on drugs aimed at reducing acidity became the standard for these conditions. This, in turn, was reinforced by the investment made by pharmaceutical companies in what proved to be widely-used drugs, some of them routinely used for symptoms of dyspepsia and dispensed over the counter.

4.3. And yet…

Enter J. Robin Warren, an Australian pathologist working at the Royal Perth Hospital. In 1979, Warren repeatedly found what looked like S-shaped bacteria in biopsies of the gastric mucosa of patients suffering form gastritis. He used procedures which were common in pathology, and identified these entities through light microscopy, using a silver staining method. These entities were definitely identified as bacteria. Warren went on to suggest that these bacteria, found in patients suffering from active chronic gastritis, could be associated with that pathology.Warren's work led him away from the mainstream in approaches to the bacteriology of the human stomach – or rather, to its "sad neglect", as Warren would later phrase it. (Warren, 1983):

> Basic medical teaching for more than 100 years stated that bacteria do not grow in a normal stomach, probably because of the acid environment. Bacteria or fungi, often *Candida*, do grow in atrophic stomachs or in the necrotic debris in an ulcer. In those cases the infection appears to be secondary to the underlying lesion and of little significance (Warren, 2002: 151-152).

This common belief was, in turn, associated with the current practices in gastroenterology and gastric pathology. Endoscopies were less common before the 1970s, and most of the specimens coming to pathology labs were stomachs sent from surgery, which were "usually unopened", with the mucosa showing "moderate autolysis". The other source of specimens

was post-mortem examination; the specimens reached the pathologist's lab only after "the enzyme and acid digestion of the tissues was well under way" (Warren, 2002: 152). Neither bacteria nor the "fine detail of the gastric mucosa" would thus be available for examination (Id.). Warren then adds an observation of considerable significance: "If medical textbooks showed pictures of well-fixed gastric mucosa, they were often animal tissues that could be fixed immediately" (Id.).

These practices made chronic gastritis a pathology difficult to diagnose, and thus it "was thought to be relatively unimportant compared with ulcers and stomach cancer" (Id.). Only those conditions which were more easily visible using available technologies, such as "gross atrophic endoscopically visible gastritis, as seen in pernicious anaemia, a classic disease beloved of medical schoolteachers, but uncommonly seen in clinical practice", tended to be identified (Id.).

Let us stop briefly to look at the list Warren provides of the beliefs, practices, technologies and pathologies which, together, configure a situation he is obviously critical of. First, there are certain ways of seeing and interpreting materials feom biopsies and other specimens constituting a "widespread belief" in the absence of bacteria as pathogens in the human stomach. Secondly, this belief is in turn associated with the characteristics of the materials available to pathologists and to the prevailing modes of describing gastric pathologies. The use of animal tissues for illustrations in textbooks contributes to these (flawed, according to Warren) descriptions. Finally, the lack of common use of technologies like endoscopy (and the limitations, up to the early 70s, of available endoscopic techniques) do not allow appropriate, "well-fixed" gastric biopsies to be obtained for examination. Together, they appear as a robust configuration.

Any change in this configuration requires, first, that its consistency, or the congruence of the elements constituting it, be challenged in an effective way, through the weakening and, subsequently, the breaking of the attachments that hold them together. Warren's work in the late 1970s will take the first steps in that direction. It will rest upon three different events. The first, which is not easily identifiable from published accounts such as letters or articles, was the enthusiastic embrace of a new classification of gastritis published in 1972 by Whitehead, Truelove and Gear, which Warren found "logical and easy to use", in contrast to previous, commonly used practices of description and classification of biopsy sections. The new classification was based on the use of "common features such as the location of the biopsy, the depth, type and severity of the inflammation, the degree of atrophy of the gastric glands and the presence of intestinal metaplasia" (Warren, 2002: 152). A feature Warren singled out which was to become particularly important to his work was the description of a "specific histological change that [the authors] referred to as `activity´ and which is a common feature that had previously been ignored. I could easily see and measure these changes and the results appeared consistent" (Id.). The second was the appearance, in the early 1970s, of a new technology for gastroscopy, the fiberoptic endoscope, which finally allowed adequate gastric biopsies to be obtained. The third, finally, was his unorthodox interest in "experimenting… with various stains for bacteria in histological sections" (Id.). Since most of the stains used for that purpose stain the tissues as well and thus make it "very difficult to see micro-organisms gainst this complex background", Warren became interested in two particular types of stain which did not exhibit that problem: the Gram stain and the Warthin-Starry silver stain. The latter was of particular interest to him, since it stained some Gram-negative bacteria. An

additional element, which we will go back to later, was electron microscopy, which greatly improved the capacity to visualize the details of biopsy sections.[28]

In June 1979, Warren had at his disposal well-fixed gastric biopsies which "showed numerous suspicious bacteria on the surface". Warren describes the event in terms which sound like the depiction of an actor-network, of an association of human actors, technologies and biological material:

> I had seen the arrival of the endoscope and the subsequent improvement of the quality of gastric biopsies. I had read Whitehead's description of gastric histology and pathology. I was experimenting with the use of the Warthin- Starry silver stain. Therefore, I ordered the stain for this case, and there before my eyes, was a beautiful silver stain, with numerous bacilli clearly visible, even on low-power magnification. (Warren, 2002: 153)

His report on this observation is of particular interest, in that it provides the first suggestion of an association between gastritis and the presence of bacteria, but also the first reference to these bacteria as having "the morphology of Campylobacter. The second section of the report, on microscopic analysis of the section, mentions the presence, on the surface of the mucosa, of "numerous coiled or curved bacilli up to about 3 um in length with up to two loose coils. Many of these are in close contact with the surface of the epithelium" (Warren, 2002: 155, Figure 2). And the conclusion states:

a) There is chronic gastritis with a small erosion. The quality of the surface mucus appears slightly more dense than normal in man areas, and it contains numerous bacteria in close contact with the surface epithelium. These bacteria have the morphology of Campylobacter. They appear to be actively growing and not a contaminant. I am not sure of the significance of these unusual findings, but further investigation of the patient's eating habits, gastro-intestinal function and microbiology may be worthwhile.

b) Mild gastritis (Id.)

The report thus brings together, in one single text, the description of a lesion in the antral mucosa of a patient and the presence of bacteria, and suggests a possible association between them, based mostly on the location of the bacteria. Warren declines to advance an explanation and recommends further investigation of the patient's condition. But he has inscribed, for the first time, the main building blocks of what was to become his first publication on the subject, a letter to the Editor of *Lancet*, published in 1983. In his 2002 account, Warren goes back to this report:

> The bacteria appeared fixed to the surface of the epithelium of an abnormal mucosa, *in a way that looked as if the bacteria were actually causing the damage*. They often seemed to be penetrating between the epithelial cells, which were bulging out in the manner of active gastritis. I arranged for thick sections from the tissue wax block to be examined by electron microscopy and those, too, clearly showed the bacteria, closely applied to the epithelial surface and appearing to extend between the bulging cells, but only as deep as the intercellular junctions (Warren, 2002: 154; italics added).

---

[28] For a detailed study of how electron microscopy was associated with key changes in what the author calls "methods of inquiry" in the life sciences, see Rasmussen (1997). Rasmussen's study explicitly draws on the pragmatist tradition and on the work of John Dewey in particular. See the discussion of the relevance of pragmatism to science studies in Chapter 2.

Even if this is a retrospective account, the text of the report suggests that the (still unspoken) possibility of bacterial infection being the cause of the observed lesion was regarded as plausible, due to the impressiveness of the visual evidence. Electron microscopy makes the first appearance in this story, and it was to become a major asset in the struggle to produce evidence of the association between gastritis and bacterial infection.

At the time, Warren's colleagues believed that the bacteria were real, but since their meaning was unclear, he was advised to look for more cases. This was sensible advice, since the reality of observations is less easily dismissed by sceptics or critics if observations are multiple. The greater the number, the less they are vulnerable to dismissal as exceptions or as artefacts of the apparatus of observation. At this point, what was at stake was the very reality of the bacteria which were observed and of their location and coincidence with a specific lesion of the gastric antrum. If any of these could achieve the status of matters of fact, resisting attempts at "undoing" them as artefacts, a first and crucial step would have been taken to shake the configuration of beliefs and practices in place. At this point, however, this was not yet explicitly stated as an objective.

Warren actually found more cases, to his amazement, as he admits, and "in smaller numbers than in the first case or showing a patchy distribution" (Warren, 2002: 154). Their close relation to active chronic gastritis, according to Whitehead's description, "became obvious", and two features were recurrent: a "specific epithelial distortion and superficial polymorphonuclear cell infiltration". Interestingly, Warren hints at the difficulties of a straightforward identification of the bacteria: "*With experience*, I found the bacteria in almost half of the biopsies from the gastric antrum, *although sometimes they were rare and often the histological changes were mild* " (Id., italics added). The ability to find the bacteria was thus linked to the experience of the observer, which presumably increased with growing numbers of observations, and they were not always found, nor in significant numbers, as expected. In how far did these limitations hamper the ability to make the bacteria and their possible significance visible to peers and to the community of gastroenterlogists? Warren seemed to be aware of how fragile his findings could become if they were to be regarded as some kind of idiosyncratic quest. He thus tried (successful) to recruit his colleagues to record findings of bacteria through coding for it in reports. The result was that the number of observations and the number of those making the observations increased to several hundreds "over the next couple of years" (Id.).

At this point, Warren had been able to recruit other pathologists to record observations of bacteria. He had been able to make the bacteria comply with the demand to make themselves visible, through appropriate staining techniques. But he could not find allies in clinicians. Clinicians, he explains, had different goals from pathologists. They were interested in biopsies taken from any part of the stomach to look for abnormalities or lesions like ulcers or tumours. Secondary inflammation or healing of the mucosa near these lesions appeared, which were unrelated to the histological condition in other parts of the stomach. They ridiculed the idea of "sending gastric samples especially for microbiological culture". The ethos of clinicians, as well as the medical doxa, in fact, appeared as an obstacle to the pursuit of Warren's interests:

> Patient care was the primary consideration, before esoteric research projects. In any case, everyone had known for a century that bacteria did not grow in the stomach. Why would a well-balanced gastroenterologist take samples from apparently normal parts of the stomach in order to look for bacteria? (Id.)

Two questions were frequently asked to Warren by clinicians when he tried to engage them in discussion. The first was: "If the bacteria really are there, why are they not just secondary to the inflammation?" The second was: "Why, if the bacteria really are there, has no-one else reported them?" Warren's answer to the first question was that as a pathologist he could not ignore that "the features, position and distribution of the bacilli had the appearance of a primary infection, with secondary mucosal damage". To the second, he had no reply at the time. Although reports of observations did exist, they had been ignored or dismissed, and Palmer's 1954 article was still regarded as the authoritative statement on the subject. Failure to give convincing and authoritative answers to these questions meant that clinicians would be difficult to get aboard, and those answers would require a huge effort to unmake the strong associations of the medical (gastroenterological) doxa and current clinical practice (Warren, 2002: 155, 157).

One year later, Warren found out that the Electron Microscopy Department of his hospital had filed a series of about a hundred images, showing bacteria, which had been found by one of his colleagues, Professor Papadimitriou, who had also produced descriptions of them. Warren tried to convince Papadimitriou to co-author a paper with him, but he declined, apparently not paying too much importance to the matter. Even those who had found bacteria seemed not to be interested in pursuing work on the subject (Id., 157). Warren thus continued his quest by himself, but following a different path. He started a study based on a negative control of filed gastric biopsies, with the aim of finding out how many of those cases coded "normal" would show bacteria. The task was difficult, due to prevailing coding practices of the biopsies, but Warren ended up finding 20 cases. He excluded one, due to a coding error, and found additional corroborating evidence of his findings. And he kept finding bacteria in about half his biopsies, "usually in biopsies with accompanying chronic gastritis showing active changes", and recording their absence "when the antral histology was normal" (id., 158).

Warren started preparing a paper and had it almost done when he met Barry Marshall, in 1981. Marshall was in training as a registrar of the Royal Australasian College of Physicians, then doing a period at the gastroenterology department, during which he was expected to complete a small research project. Marshall became the crucial ally Warren needed to find the missing link of the relationship between the results of histology and bacteriology and what was going on with patients.

By 1981, when Marshall and Warren meet, the alignment of actors in the unfolding drama of bacteria in the stomach thus looked as follows:

- Robin Warren, a "soft maverick" pathologist
- Barry Marshall, a young physician
- Bacteria in biopsies of the gastric mucosa, observed by Warren, and apparently associated with active chronic gastritis
- Staining techniques allowing bacteria to become visible
- Electron microscopy, increasing the visibility of bacteria and of their location
- Microbiologists helping with processing and culturing of the bacteria

• Gastroenterologists, most of them aligned with orthodoxy and skeptical of Warren's findings and early claims

4.4. From the laboratory to the consulting room and back

Marshall's arrival allowed a collaboration to be set up, based upon a partial convergence of interests:

> I was interested in Robin's bacteria because, as he and I both knew, the stomach was supposed to be sterile. I did not know it then, but he had tried to recruit others into the work for some time, without success… I had no particular opinion as to the pathogenicity of the gastric organisms, but I was aware of publications in the literature describing Campylobacter jejuni as a newly discovered common cause of food-borne gastroenteritis and colitis (Marshall, 2002b: 169-170).

At this stage, Warren still had to persuade Marshall of the plausibility of the pathogenicity of bacteria in the stomach. Though Marshall, as he himself states, had "no particular opinion" on the matter, he was open to a collaboration aiming at the organization of the trials which would put to the test the possibility advanced by Warren on the basis of his previous results. As he himself admits, in a long conversation with Warren, "he [Warren] presented such a good case for the bacteria as pathogens that I accepted the concept rather naturally after that". After all, "a new species of bacteria would make a nice publication, regardless of whether or not it actually caused a disease" (Id.).

Marshall's contribution to the collaboration included the crucial task of linking their work to the literature for "previous references to the curved bacteria". He thus came across a series of reports of observations of similarly shaped organisms, going back from Susumu Ito's Handbook of Physiology to Vial and Orrego, Salomon and Bizzozero, Freedberg and Barron and Doenges, the latter three articles identified through a citation in Ed Palmer's influential 1954 article. His first reaction was one of disappointment to "see that `our´ spiral bacteria had probably been described before. On the other hand, linkage with gastritis was not a major feature of the previous literature, because most of the studies were animal, post-mortem or gastrectomy material" (Marshall, 2002b: 170).

This observation points to a crucial aspect of the making of scientific objects which has been put at the core of approaches like ANT and, more generally, of approaches in science studies and history and philosophy of science inspired by pragmatist philosophy: scientific objects are defined not through some intrinsic or essential properties, but through their *attachments* or their *effects*, i.e., what they do.[29]This strategic point was well understood by Warren and Marshall, who did not just focus on the bacteria and their morphology, but, also, from very early on, on their associations with gastric pathologies.

Still, the efforts towards the identification of the bacteria observed was not dropped, and Marshall's literature searches included the growing body of publications on what were then called "Campylobacter-like organisms" (CLOs) found in humans. His literature review revealed that some of the recently identified species were commensals, which raised doubts, again, on the possible status of "their" bacteria as pathogens (Id., 170).

---

[29] See the discussion in Chapter 2.

Further literature searches drew attention to studies of gastric biopsies in people with "normal" stomachs. This was, again, to become a key direction for subsequent work, since Warren and Marshall were interested in the prevalence of spiral-shaped bacteria among members of the population who had not been diagnosed with gastric pathologies. This required the capacity to recruit "healthy" stomachs for study, since "Robin's biopsy series had been chosen for him by the gastroenterologists investigating abnormal endoscopy findings" (Id.).

Marshall worked on Warren's first 25 records, coded them and expanded the study to include clinically relevant information obtained directly, when possible, from those patients. He was increasingly convinced, as was Warren, of the need to work on fresh biopsies obtained through a targeted, specifically designed study, and to culture bacteria from them. Warren asked Marshall for "clean biopsies" from areas of the gastric antrum not affected by lesions, rather than routine biopsies, which were less appropriate for examining the histology of gastritis. Marshall recruited 20 patients from those attending endoscopies and who were suspected of having gastritis. Extra biopsies were taken from "areas of the gastric antrum that looked normal to the endoscopic eye". Both bacteria and active gastritis were common in these sections. According to Warren, this led Marshall to enthuse about continuing research (Warren, 2002: 159).

Marshall was able not only to enrol patients, but he also enlisted the collaboration of the Department of Microbiology of the Royal Perth Hospital, where a routine was established for the culturing of spiral shaped bacteria based on previous experience with *Campylobacters*. Although the use of Gram staining revealed Gram-negative bacteria with the expected spiral shape, attempts at culturing the micro-organism over a period of 6 months failed, despite the use of a range of variations in media and atmosphere (Marshall, 2002b: 173).

Meanwhile, a significant episode took place, in October 1981: the first successful treatment with an anti-infectious therapy of a patient complaining of severe stomach pain and exhibiting both inflammation of the stomach and spiral-shaped bacteria. As CLOs were known to be sensitive to tetracycline, this was used to treat the patient. The attending physician and the patient agreed to try that treatment and to undergo a new endoscopy and biopsy after two weeks. The symptoms disappeared, and "[t]he patient (…) was ecstatic in his discovery that an antibiotic treatment was able to completely eliminate his extremely severe and chronic gastric symptoms" (Marshall, 2002b: 173). For Marshall and Warren, however, the outcome of this case was far from clear. The stomach still showed signs of inflammation, but there was an improvement in the histology and the bacteria had disappeared. And with just one case it would be impossible to make a strong case for the effectiveness of antibiotic treatment, since there was still no evidence that the bacteria were the cause of the problem afflicting the patient. This episode, however, had two further consequences. The first was the decision to proceed with a study on a larger scale. The other was that the way Marshall and Warren were proceeding put them at risk of being charged of ehical violations, with the possible consequence of alienating patients, their colleagues and the hospital administration, and would be just impossible to keep for that larger study:

> This was the first time I realized that our clinical research project was probably overstepping the bounds of what would normally occur in the management of a patient, and therefore might reasonably be the subject of ethics committee consideration. Taking an unnecessary biopsy was one thing, but using obscure findings from that specimen to justify antibiothic therapy was another. (Marshall, 2002b: 173)

In 1982, a pilot study was proposed involving 100 patients, recruited consecutively among those referred for gastroscopy, which would be "the baseline for a more elaborate trial with a control group and incorporating follow-up endoscopy and biopsy after treatment of affected patients with the appropriate antibiotic" (Id., 175).[30]The questions the project intended to answer, as stated in the protocol, were the following:

> Is the observed bacterium present in normal stomachs? Can the presence of the bacterium be correlated with the type and severity of the gastric pathology? Can the organism be cultured? In those patients who undergo a further gastroscopy and biopsy for whatever reason, does persistence or disappearance of the organism correlate with the patient's symptoms? (Marshall, 2002b:175)

All participants were volunteers, and informed consent was required. Different procedures were mobilized for this study, including a questionnaire on a range of conditions possibly associated with bacterial infection, gastroscopy, histology, electron microscopy and, after coding of the results, statistical analysis. The questionnaire focused on "symptoms, medication use, diet, pets and travel". Interest in these topics arose from some educated guesses by Marshall on the possible origins of the bacteria. These included contamination by animals, lodging of the organism between the teeth of humans, presence in milk or dairy products, decreased protection of the human stomach against infectious agents because of the widespread use of acid-reduction drugs, a micro-organism brought by tourists to Australia from Asia, or even some unknown and unexplained event. There was speculation as well on whether the micro-organisms were specifically Australian (Marshall, 2002b: 174). For each patient two biopsies were, one for Warren, for silver staining, and the other for Gram staining and culture in the microbiology laboratory. The first would comply both bacteria to show themselves and histological details to become available for the pathologist. The second biopsy would allow the bacteria to be further "disciplined" in the lab through culture.[31]

One of the first, surprising results of this study was the dissociation between reported symptoms and "histological gastritis" as diagnosed by the pathologist on microscopy.

The bacteria found in the study were cultured with the same techniques used for the culture of Campylobacter - bacteria usually cultured from fecal samples -, since Warren had suggested that there was a resemblance between these and "his" bacteria. The difference was that the antibiotics used in the standard procedure were dropped. Cultures were left for the usual two days in the microaerobic culture cabinet and then examined and, if they exhibited no "unusual organisms, they were discarded" (Marshall, 2002b: 177). This was routine practice for "feces cultures or throat swabs", and, in a situation of severe understaffing of the laboratory due to an epidemic of an infectious agent in one of its wards, the job was performed by junior lab technicians who followed the routine. Initially, all cultures were negative. Due to an oversight, one of the biopsies was left over a 5-day holiday in a microaerobic culture cabinet. It was later found that colonies had formed on the plate which, when transferred to a slide and stained, showed the presence of bacteria. Electron microscopy allowed the

---

[30] The design of the study was presented in detail in a paper published in 1984 (Marshall and Warren, 1984). See Chapter 3 for a detailed discussion.

[31] Recruiting patients and retaining them for the whole duration of projects which involve submitting to not so pleasant and invasive procedures as endoscopy is certainly not an easy task, and defection of these crucial allies is highly likely. As Warren noticed, however, "Barry's ability to retain trial patients was quite amazing. He encouraged them to return again and again and again for what is a relatively uncomfortable investigation – even when they did not have symptoms! In the whole study, only one patient missed one gastroscopy on one occasion" (Warren, 2002: 162).

morphology of these bacteria to be examined in detail and it was established that they were spiral-shaped, similar to *Campylobacter*, except for the presence of four flagella of unusual shape. Other positive cultures were obtained, and it was found that "the incubator was leaking and once we repaired it, cultures suddenly became very reliable for diagnosing the presence of this organism" (Warren, 160).

Although Marshall had to leave, before completion of the study, to Port Hedland, a small town 2000 km to the north of Perth, he "completed the organization for the trial, persuaded clinicians to have their patients fill in our detailed questionnaires, and collated all clinical findings with my histology report" (Id.). Marshall took with him the endoscopy reports and collated them. He discovered, to our mutual surprise, that I had found the bacterium in all 13 patients with duodenal ulcers, and 24 of 28 gastric ulcer patients. Thus we could show that the bacteria were related to the 'active' type of chronic gastritis, that they could be cultured and were a new variety of bac-terium, and that they were related to peptic ulcer and very strongly to duodenal ulcer. The latter was rather unexpected (Id.).

This admittedly unexpected association of the bacteria with two kinds of ulcer was to become a further step in strengthening the associations needed for the observed bacteria to become an active agent of infection. The next step was to publish these results, preferably in a major medical journal. Marshall proposed that a letter with descriptions of the findings be sent to *Lancet*. Warren took up that task, writing a summary of an unpublished paper reporting on his early findings. Marshall thought that the letter did not contain anything that might count as "new" and so proposed to write a companion letter with a preliminary description of the work they had done jointly. Both letters were sent to Lancet and published in 1983, after some discussion with the editor (Warren, 1983; Marshall, 1983).[32]

At this point, new and powerful allies join the Warren and Marshall: the patients who voluntarily submit to gastroscopy. This, in turn, is the result of Marshall having joined Warren. Microbiologists, who face the challenge of processing and culturing specimens, are a further ally. But a contingent event turns what might have amounted to a failure into a success: a failing piece of equipment and an oversight that results in leaving a culture in the microaerobic cabinet over a five-day period unexpectedly contribute to success.

Warren and Marshall now hold the resources they need to launch a first explicit challenge to the prevailing doxa and to show that their results are plausible. In other words, they *problematize* the current approach to the explanation of gastric disease by establishing, first, that bacteria do grow in the gastric mucosa; secondly, that they are co-present with histological features of active chronic gastritis; thirdly, that both findings hold for biopsies of the antrum taken from a statistically significant number of patients; and, finally, that the conditions associated with the presence of bacteria identified through histological examination may not be associated with symptoms. Each of these claims directly challenges the gastroenterological establishment. But this is not enough for these claims to be turned into matters of fact acknowledged as such by those who are challenged and robust enough for new allies to broaden the actor-network which is in the process of constituting itself.

One of the steps still missing was that of publication in peer-reviewed journals and/or presentation at scientific conferences. Publication confers to claims or statements the status

[32] For a detailed discussion, see Chapter 4, supra.

of truth claims which have successfully overcome the predicament of their evaluation by peers.

Publication, however, is just one part of the tasks ahead. Warren and Marshall have to show that the interests of the actors lie in accepting their claims and following the course of action they propose to diagnose and treat gastritis.

For patients, this means the prospect of more accurate diagnosis and better treatment. For colleagues, more effective ways of describing the etiology of, and diagnosing and treating, common gastroduodenal diseases.

They also have to persuade bacteria to show their existence and to display the properties they endow them with. In other words, bacteria have to be disciplined. But disciplining micro-organisms (or other research objects, for that matter) requires, first, that they be allowed to react to the challenges experimental settings pose to them. Successful domestication of bacteria will turn the procedures developed by Warren and Marshall into obligatory passage points for those searching adequate diagnosis and treatment.

Throughout this process, and despite the successes in enlisting a range of different actors to their positions, Warren and Marshall still had to face the formidable opposition of gastroenterologists.

4.5. Locking allies into place

In order to align and "lock" their allies into the places and roles they have assigned them, Warren and Marshall needed the identities of these actors to be stabilized. This, however, proved not to be an easy task. Bacteria resisted displaying the properties assigned to them, and behaving as they were expected. Patients, even when initially compliant with diagnostic procedures or treatment, could decide to leave trials or to refuse complying with treatment if the latter was not successful. Colleagues could dissociate themselves from or be openly hostile to the propositions advanced by Warren and Marshall. Equipments might refuse to work properly. Different forms of resistance and conflicting loyalties might thus lead to the rejection of these propositions. They had to "build devices which can be placed between [*inter esse*] [their prospective allies] and all other entities who want to define their identities otherwise" (Callon, 1999: 72-73).

This means that, first, they have to weaken the links between colleagues and the prevailing orthodoxy in gastroenterology; secondly, that they have to weaken the links between patients and conventional therapies of common gastric diseases; third, that they have to weaken the invisibility and unresponsiveness of bacteria to the trials they are subject to. Next, they need to persuade their colleagues that bacterial infection is the cause of common gastric diseases, and persuade patients that their interest in getting accurate diagnosis of their ailments and effective treatment and, eventually, a cure, would be better safeguarded through their approach.

Both these operations require that the demonstration be made in a way that is resistant to criticism, by showing, first, that the bacteria they claim to exist in the gastric mucosa of patients do exist, that they are not effects of contamination or artefacts; next, that they are the cause of infection associated with the diseases, not commensals; third, that the effective response to at least some forms of common gastric diseases, such as gastritis or peptic ulcer disease is therapy for infection, not anti-acid treatment. A further step is required, without which these three steps are still vulnerable to criticism and their association may be weakened:

to link these findings to the relevant, existing bodies of literature, namely through the identification of references to observations of gastric pathologies and to reports on spiral shaped bacteria in the gastric mucosa, by establishing a link between these two bodies of literature and proposing a plausible and robust way of associating them through some explanatory mechanism.

This is where publication becomes a key strategic move. Between 1982 and 1984, Warren and Marshall turn the *inscriptions* produced through their work – laboratory notes, pathology reports, questionnaires, protocols, reports from observations, micrographies, graphs… – into drafts of letters, articles and papers to be sent to peer-reviewed publications or to scientific conferences (Latour and Woolgar, 1986; Latour, 1987). This, however, stumbles on some obstacles:

> In October 1982, I presented the preliminary findings from our study to the local College of Physicians meeting, where it received a patronizing and mostly negative response. The main objection from the gastroenterologists was that our study had found a strong correlation between gastritis in the stomach and ulcer in the duodenum. This seemed out of place and incorrect, because `everyone knew' that gastritis was associated with gastric ulcers, but not especially with duodenal ulcers. I had no answer for this criticism, as I was not formally trained in gastroenterology and my reading (apparently selective) had taught me that gastritis was more likely to be associated with duodenal ulcers than with gastric ulcers. (Marshall, 2002b: 180)

These criticisms prompted Marshall to look again at published studies, which showed that, contrary to expectation, "duodenal ulcers seemed to be more strongly associated with gastritis than gastric ulcers, a `paradox´ the "ulcer research community seemed to have skipped over. This fact did not mesh well with the current understanding of peptic ulcer etiology, and had therefore been ignored. Was gastronterology a science or a religion? I decided it was the latter" (Marshall, 2002b: 180-181).

In 1981, both Marshall and Warren were aware of the need to publish their findings before someone else beat them to the printed record. But putting together the first publications proved to be a not so simple endeavour. Warren and Marshall offer non-coincident (though not necessarily incompatible) versions of how the two letters (mentioned above) which provided early reports on the findings appeared and how they finally got published. According to Warren, he wanted to write a "definitive report", but Marshall thought that an advance letter should be sent to *Lancet*. Warren thus wrote a summary of a paper he had written but never published, but Marshall thought that "there was nothing new in it" (Warren, 2002: 160). Marshall thus wrote a second letter and negotiated with the Lancet editor the joint publication of both letters.[33] The version given by Marshall is that he "attempted to construct a letter to The Lancet concerning our data and mailed a first draft" of it to Warren, getting no reply for severaI weeks. The letter was discussed by phone and correspondence was exchanged. According to Marshall, Warren was "concerned that a joint author letter made it appear that I was also involved with his original observations of spiral bacteria and gastritis" that he had made before they met (Marshall, 2002b: 181). Marshall replied claiming the main credit for "our present understanding of the importance of the organism (i.e., that it could be etiologically related to peptic ulcer and gastric cancer". His supervision of the endoscopic, microbiological and clinical work, as well as his literature review, had in fact created what we

[33] See Chapter 3, supra.

might describe as the strong associations making their work credible, "allowing us to be forceful and place our observations in a top medical journal, rather than a more specialized pathology journal" (Marshall, 2002b: 181). He later admitted to be feeling "rather paranoid and very isolated in the remote town of Port Hedland", and refers to his disappointment when he noticed that in the protocol for their joint study Warren had planned to publish in a pathology journal and that he had decided to send a letter solely authored by him to *Lancet*. He suggested to Warren that his letter would have to be "sanitized" to avoid "stealing the thunder" of their collaborative work (Marshall's words). After negotiation with the Lancet editor, they sent two separate letters, to be published in the same issue. This seems to have been one of the key moments at which the strong associations the two Australians were struggling to construct appeared to be more vulnerable (Id., 181-182). The story did not end there, since the editorship of Lancet raised the issue of why there were two separate letters. This was finally solved with Warren describing his early findings and Marshall reporting on their joint work. Marshall's irritation with the microbiologists in Perth (the lack of urgency with which they treated their samples, the oversight in the culture, the leaking incubator, and later a discussion on authorship with one of the microbiologists) encouraged his claims to have been responsible for the bulk of the work that mattered and thus were additional reasons for him to decide to sign as the single author the letter on their joint work. The letters were finally published in June 1983.

At his new job at Fremantle Hospital, Marshall initiated a collaboration with David McGechie, a microbiologist, and another pathologist, Ross Glancy, which allowed him to pursue the collection of biopsies of the gastric mucosa and the culture of bacteria, successful in 90% of the cases where they were observable in histological sections. That was when Marshall started corresponding with gastroenterologists in Europe and in the United States, on observations which appeared similar to or convergent with his own and which led to positive results when they identified spiral bacteria in patients' biopsies and successfully cultured them.

In spite of these early international collaborations, though, the relationships with the gastroenterological establishment in Australia were still difficult, to say the least:

> In February 1983, Robin Warren and I wrote an abstract for submission to the Gastroenterological Society of Australia meeting, which was to be held in Perth (…). We were sure the abstract would be accepted and, because the meeting was local, it would cost us very little to attend the conference and .present it. Regrettably, however (…), our abstract was not accepted, with the condolence letter from the secretary stating that, 'of 67 abstracts submitted we could only accept 56', thus our material must have been rated in the bottom 10%! (id., 184)

Microbiologists, in contrast, seemed to be increasingly interested in the newly found bacteria. In 1983, Marshall was invited to submit an abstract to the Campylobacter Workshop, to be held in Brussels, where he delivered the first version of a paper co-authored with Warren and published the following year in The Lancet (Marshall and Warren, 1984). The path to publication, again, was winding, due to the difficulty of finding reviewers for the article who would "agree that our paper was important, general enough and interesting enough to be published. The article was finally accepted in May and published in June 1984, with an editorial underlining its relevance, accompanied by several letters, all reporting corroborating findings (Marshall, 2002b: 193-194).

By 1984, several accomplishments could be credited to Warren, Marshall and their collaborators:

• Warren had shown that spiral shaped bacteria could be found in the stomach mucosa

• These bacteria were found in patients with several types of common gastric disease, including active chronic gastritis and peptic ulcer disease

• They were not found where these conditions were not present

• Their morphology had been described, showing a resemblance to known *Campylobacters*, but also some significant differences which suggested that the might be a new species or even be part of a different genus

• There was some evidence, though still weak and isolated, that antibiotic treatment could be effective for conditions where the bacteria was present.

This meant, in turn, that the bacteria now had the status of real organisms, of facts established by observation, that they could be related to other existing bacteria and that they were associated with common gastric diseases, although the nature of these associations had not been established. All of these attributes were, in fact, the outcome of specific, active associations (Fleck, 1979/1935) of the bacteria with other entities, in the laboratory (culture media, atmosphere, electron microscopy) and in clinical settings (patients, gastric pathologies, endoscopes). The bacterium itself was becoming an obligatory passage point for a heterogeneous assemblage of human actors, which included pathologists, microbiologists, some clinicians, electron microscopists and patients who underwent endoscopy and biopsies. Still missing was, however, the strong association between bacteria and disease which would weaken the doxa and the loyalties of the gastroenterology community and thus open the way to the emergence of a new approach, with that association as an obligatory passage point for researchers and clinicians beyond those who were already "on board". In order to accomplish this, a further step was needed: transform the question of the nature of that association into a series of statements which were more certain (Callon, 1999).

4.6. "Transforming the question into a series of statements which are more certain"

The association between the bacterium and diseases like gastritis or peptic ulcer had not been demonstrated to be a causal one. In order to make that demonstration, it was necessary to move on to a different research design, one that was experimental. Since the purpose of that next step was to put to the test the causal association between infection by the bacterium and disease, the design of the experimental procedure could be based on a time-honoured approach in bacteriology, regarded as one of the main victories of science over disease and pathogenic agents. The approach was the experimental fulfilment of Koch's postulates. Formulated in what was to become their standard form by Koch's colleague Loeffler in the late 19th Century,

Koch's postulates define the four requirements for demonstrating that a specific micro-organism is the cause of a specific disease:

> I - Showing that the organism is always found in diseased animals (including human beings), but not in healthy ones
>
> II - Showing that the organism can be isolated and grown in culture
>
> III - Showing that the organism grown in culture initiates and reproduces the disease when innoculated into susceptible animals (including human beings)
>
> IV - Showing that the organism could be re-isolated from inoculated animals (or human beings)

Koch's first postulate had been fulfilled by the studies conducted by Marshall and Warren in 1982 and 1983, especially through the large pilot study in Perth. It had been shown that the bacterium was present in patients diagnosed with gastritis and with a form of peptic ulcer disease, but was not found in those not diagnosed with those conditions. The results supporting this claim were to be found in the article published in Lancet in 1984 (Marshall and Warren, 1984).

The second postulate was fulfilled through the isolation and culture of the bacteria from biopsies, and reported by Marshall and Pearman, in 1984.

Koch's third and fourth postulate were still to be demonstrated. They would bring to the picture the two strong statements still missing: that, in this case, people could be inoculated with the cultured organism and thus contract the disease, and that the eradication of the organism would lead to the healing of the person.

The difficulty with this next step, of course, was that there were ethical barriers to the deliberate contamination of persons with the cultured bacterium. Even the use of volunteers would raise problems as to the legitimacy of deliberately exposing them to disease. This appeared as a lot more problematic than the comparatively benign practice of performing additional biopsies or experimenting therapies with antibiotics that had been a matter of some concern for Warren and Marshall. Without that step, however, it would be difficult to produce the strong and more certain statements needed to establish as a matter of fact the causal link between bacterial infection and disease. The use of animal experiments was not a sastisfactory outcome, since the animals most likely to be used as models seemed not to be affected by the bacterium. In any case, even positive animal experiments would be too weak to bring forward Warren's and Marshall's claims against the gastroenterology doxa, and the problem was compounded by their obvious lack of scientific authority, especially Marshall's, due to his job, place of work and job status:

> It was already apparent that we were not going to get an objective audience. Everything we claimed flew in the face of accepted dogma. It was undercutting the basis of gastroenterology, which had experienced a funding boom with the advent of the H2 receptor blockers, the world's most widely used drugs. It didn't help that I was a 31-year-old, living in the most isolated city in the world, who did not have a university job even in my home town. (Marshall, 2002b: 185)

Attempts at getting support from pharmaceutical companies manufacturing drugs for ulcers, public funding agencies or even a family business were unsuccessful. Marshall thus failed to enrol one of the most powerful allies he could get, the pharmaceutical industry. The reasons for that were clear to him:

> No-one was interested in revolutionizing the world of gastroenterology, partly because the concept was so outlandish [this would be the typical response of scientific institutions] and partly also because there was very little pharmaceutical research being undertaken in Australia at the time, with nearly all drug companies acting as subsidiaries of American- or European-controlled entities. Therefore, funding for new projects required substantial applications from substantial individuals with long lead times. (Marshall, 2002b: 185)

The exception was an Australian company, Gist-Brocades Pharmaceutical Company, which sent information on a product, DeNol, which was a compound containing bismuth, successfully used in the treatment of duodenal ulcers. As Marshall found out, bismuth had been used as a bactericide for a long time… Marshall even started a study with patients treated with bismuth, but with no clear results. Marshall, however, later found that a joint use of an antibiotic (metrodinazole) and bismuth had, apparently, successfully eradicated spiral bacteria from patients with gastritis and peptic ulcer (Marshall, 2002b: 188-189). Bismuth later was to become one of the components of standard eradication therapies for *Helicobacter pylori*.

In spite of these difficulties, in January 1984 Marshall managed to stay for an extra year at Fremantle Hospital and work full time on research on the bacterium, but with no funding. During that time, Marshall treated patients with gastritis and with gastritis and peptic ulcer, and successfully used a treatment for eradicating the bacterium, based on a combination of bismuth with an antibiotic (amoxycilin, erythromycin or metronidazole).

Meanwhile, he started a collaboration with a colleague from Royal Perth Hospital, Stuart Goodwin, in experimental work with pigs, trying to infect them with the bacterium. The pig was chosen as a model because "it also suffers from PUD [peptic ulcer disease] and was large enough to easily take an endoscope. Our experiment merely consisted of biopsying and culturing gastric mucosa at baseline and at periods after inoculation" with bacteria of human origin (Id., 192-193). Pigs, however, proved to be unreliable allies, since, after a few months, researchers "could not isolate the bacteria from the pigs and no gastritis developed during the experiment." Pigs also grew and became increasingly unmanageable, thus making endoscopy a difficult operation. Besides, bacteria were not collaborating, either: the target bacteria could not be cultured from pig biopsies, although the opposite happen with "all manners of campylobacters" (Id.: 193). Although Marshall does not comment on that, the failed experiments with pigs once again showed how unlikely animal experimentation was to provide the necessary evidence for the pathogenic effects of the bacteria. In fact, some earlier published observations by Warren had already hinted at the problem that the bacterium seemed to display an association with disease which similarly shaped bacteria, which had been thought to be related to the ones he observed, did not show. Animal experimentation was definitely not a reliable resource for the attempt to prove causality.

In the spring of 1984, Marshall discussed with two of his colleagues the possibility of fulfilling Koch's postulates through self-experimentation, by swallowing the bacterium. The colleagues were "noncommittal about the experiment", and Marshall did not insist. This, in fact, would be one way of getting around the difficulties in finding subjects for such as an experiment, even though objections from the ethics committee would still be likely. One day, in early June, Marshall arrived early at the hospital and asked one of his colleagues to perform

an endoscopy on him. No questions were asked, and the outcome was that Marshall's stomach was normal, with no signs of gastritis or infection. Later that day, the bacterium was cultured from a patient with a diagnosis of active gastritis, confirmed through histology. The organism was subject to a test of sensitivity to metronidazole, and the patient was treated with bismuth and metrodinazole – successfully, since one month later he showed no infection. Meanwhile, a solution containing the cultured organism was prepared by a lab technician and, after taking cimetidine (to reduce the secretion of acid), Marshall swallowed the solution. A week later, he woke up with nausea and vomiting, and this lasted for three days. The "vomitus consisted mainly of clear secretion without any acid". On the 10th day after the experiment, a second endoscopy was performed, and Marshall felt "very uncomfortable" and "gagged excessively during the procedure" (Id., 195). The biopsy section stained Gram positive and the organism was isolated and cultured for the next three days. Histology reports confirmed inflammation of the mucosa with polymorphs present in the epithelium, inflammatory cells in the lamina propria and some mucin depletion, among other alterations. Spiral bacteria were visible. The presence of the searched-for Campylobacter-like organism was thus confirmed. Two weeks after inoculation, Marshall treated himself with tinidazole. Another endoscopy showed that the spiral bacteria had disappeared (Id., 195-197).

On the basis of this self-experiment and of its results as well as of a casual encounter, in an old medicine textbook,[34] with a description of symptoms similar to the ones he had experienced, and which the authors of the book associated with what they named "gastritis with hypochloridria", Marshall wrote a paper, which, in its final version and listing as co-authors some of the colleagues who helped him with the experiment, he submitted the following year to the *Medical Journal of Australia*.[35]

Marshall's self–experiment amounted to the fulfilment of the third and fourth Koch's postulates, thus providing, at last, the long-awaited strong statement on the pathogenicity of the bacterium.

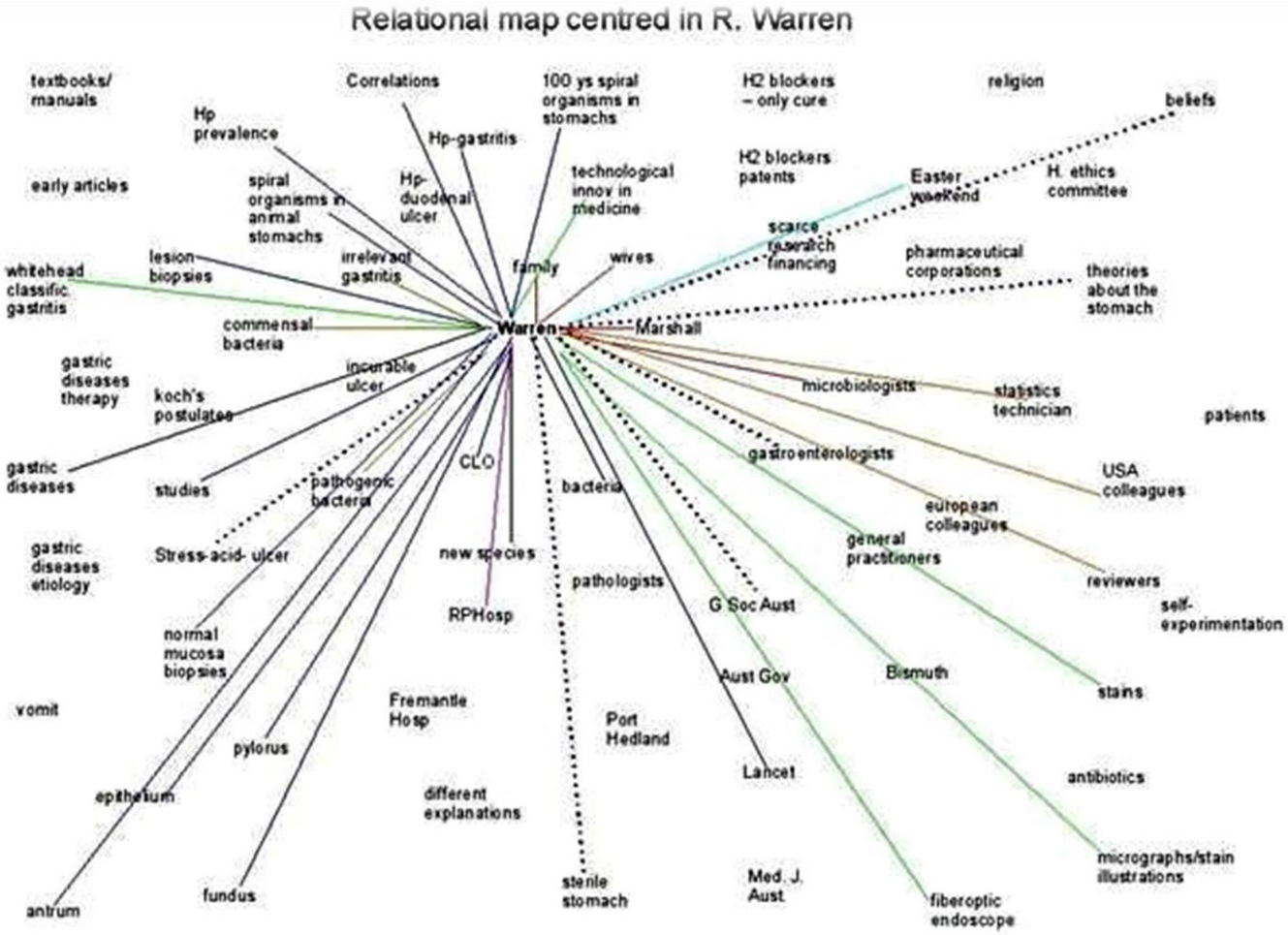
After the publication of the paper in the *Medical Journal of Australia*, the bacterium observed by Warren had become a pathogen, and it had been shown that it could be eradicated through a treatment combining an antibiotic and bismuth. Warren and, in particular, Marshall became the legitimate spokespersons for the bacterium. In the years to follow, the bacterium would be recognized as species on its own belonging to a genus different from Campylobacter, and finally christened, in 1989, *Helicobacter pylori*.

By 1985, the bacterium had gained in reality and "factness". Its effects, at the time, had highlighted its strong associations with the gastric mucosa and with pathological alterations of the stomach. But Marshall and his collaborators had shown as well how these associations could be unmade, due to the sensitivity of the bacterium to antibiotics. Patients suffering from gastritis or peptic ulcer disease were strongly attached to the bacterium through infection, which required clinical and laboratory activities to be enacted as a condition that could be treated through the "unmaking" of that attachment. All the attributes were displayed, in fact, through diverse and successive enactments of the bacterium by means of a range of clinical and laboratory procedures, but also of textual performances. In fact, the reality of the bacterium owed as much to the former as to the latter, or rather, to the way the inscriptions

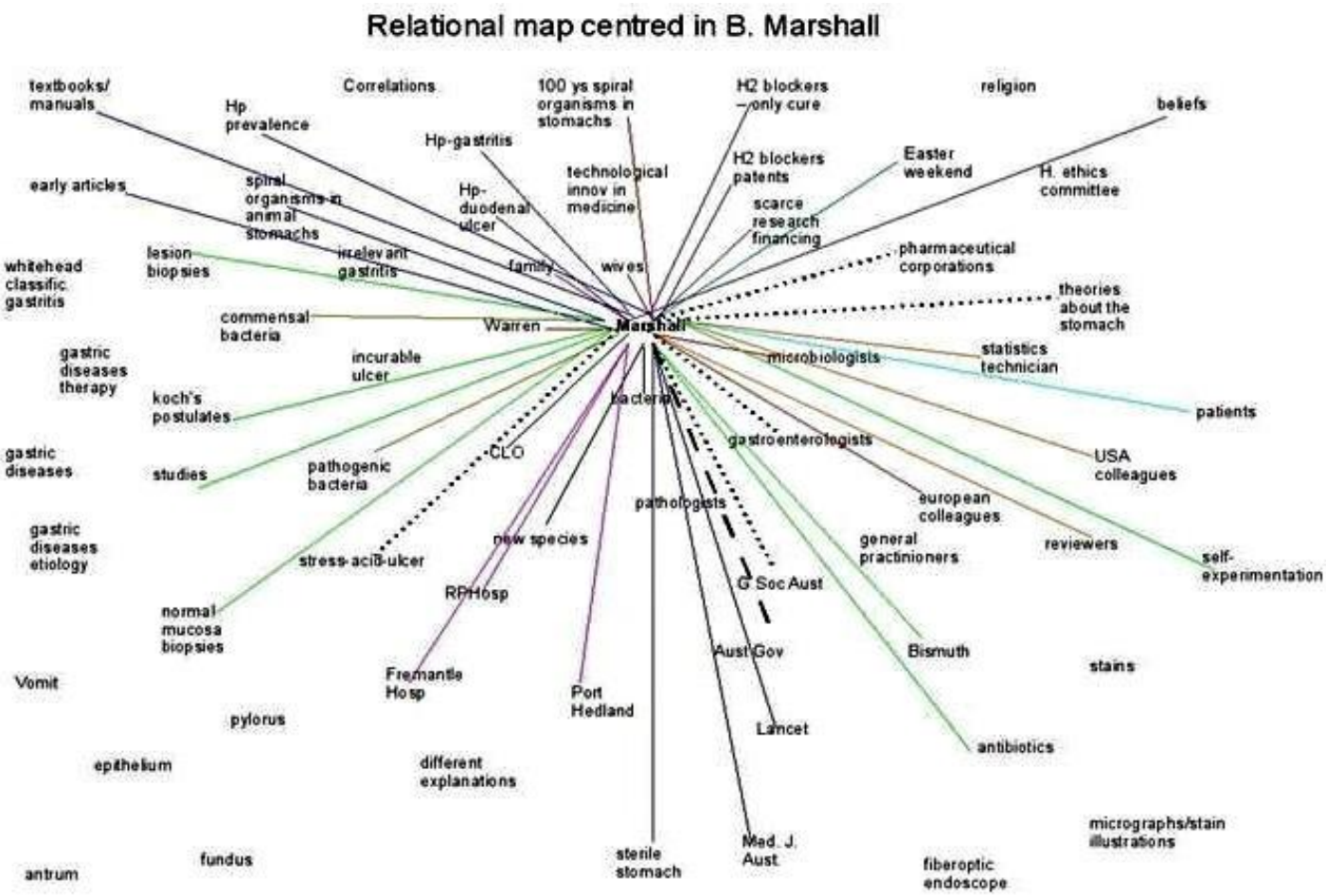
[34] The book was a 1919 edition of Osler's Principles and Practices of Medicine.
[35] See Chapter 3 for a discussion of this paper.

produced by the former were displaced into the latter, turning the bacterium and its associations or effects into circulating, shareable matters of fact. Rather than a stable entity which was "always there", the bacterium was, in fact, characterized, throughout this story, by a changing ontology, an "ontology on the move" inseparable from the modes of enacting the bacterium as a biomedical entity.

Appendix to chapter 4



Legend: Blue- evidence; Red- support/collaboration; Rose- place; Green- visualization of bacteria; Olive green- explanations; Orange- confirmation; Light blue- luck; Dashed lines – doubt, denial, obstacles.



Legend: Blue- evidence; Green- tools to produce evidence; Dashed lines- doubt, denial; Magenta- Obtacles; Light blue- therapy, collaboration, trust; Red- support/ collaboration; Olive green- different explanations for presence of bacteria; Orange – confirmation; Rose- places; Turquoise blue – luck.

The figures represent relational maps centered in R. Warren and B. Marshall, built upon situational maps. Situational maps start by identifying and listing all the elements involved in the situation under analysis – actors, actants, symbols/ discourses. Situational maps provide a view of the situation under study based on definitions by the actors involved and as subject to reconstruction by the researcher. Relational maps are built from situational maps by drawing and characterizing the existing relations between, in this case, an actor and all the elements mentioned in his/her accounts. Relational maps have allowed us to visually represent the accounts by Warren and Marshall on the discovery of H.p. in all their richness and complexity. They were also fundamental to the analysis and the building of one possible composite narrative of the history of the "discovery" of H.p. For further discussion, see Clarke (2005, especially Chapter 3).

5. Scientometric analysis

5.1. Introduction

Bacteria have been suspected to inhabit the stomach of humans since the early days of bacteriology, back in the 19th Century. However, during most of the 20th century, but particularly from the 1950s onwards, gastroenterology came to be dominated by the idea that the acid and inhospitable environment of the stomach would prevent the survival of any kind of micro-organism. Only in the early 1980s was this dominant approach shaken and a new consensus started to take shape on the role of bacteria in common gastric diseases. The turning point followed the work of pathologist Robin Warren and physician Barry Marshall at Perth Royal Hospital, Australia, who identified bacteria in gastric biopsies of patients with gastritis (Warren, 1983; Marshall, 1983). Twenty-two years after the confirmation of the presence of bacteria in the stomach, the crucial relevance of the discovery and research on *Helicobacter pylori* (H.p) was acknowledged when, in 2005, Robin Warren and Barry Marshall were awarded the Nobel Prize for Medicine for their work on *Helicobacter pylori*.

This chapter has two aims. The first is to attempt to map the research on H.p. based on the published output registered in Science Citation Index (SCI), highlighting the major trends in publication in this specific research field. The second is to offer a first inroad into the analysis of the most important international collaboration initiative in the field of H.p. research, the European Heliocbacter Study Group. Scientometrics was the privileged resource we drew upon to measure and quantify the dynamics of scientific activity, based on bibliometric indicators. The purpose of its use was, first, to identify and analyse the most productive and most cited authors and co-authorships, central papers, publications, keywords and titles, as well as the evolution of some of these indicators and how the publication record responded to controversial moments; and, secondly, to provide a first look into the composition, content and dynamics of the European Helicobacter Study Group.

Let us start with a brief reminder of what *Helicobacter pylori* is and of the story of its emergence as a biomedical entity.

The bacterium successively named pyloric campylobacter, *Campylobacter*[36] *piloridis*, then Campylobacter pylori and finally *Helicobacter pylori* is a spiral-shaped, Gram negative bacterium,[37] which colonizes the gastric mucosa and is associated with a set of common pathologies of the gastroduodenal region.

Helicobacter is a widespread infectious agent found in different parts of the world. Its presence is associated with gastritis, although most of the infected people are asymptomatic. Only a small minority develops other diseases such as duodenal ulcer and gastric cancer, but the circumstances leading to these outcomes are still debated.

---

[36] Campylobacter is a genus of Gram negative bacteria. Motile with either uni- or bi-polar flagella, the organisms have a somewhat curved, rod-like appearance, and are oxidase-positive. At least a dozen species of *Campylobacter* have been implicated in human disease, with *Campylobacter jejuni* and *Campylobacter coli* the most common (Ryan and Ray, 2004).
[37] Staining is a technique for the identification of bacteria in histological sections. Gram negative bacteria do not retain the violet stain used in Gram's Method.

Koch's postulates were tested for H.p. in several diseases of the gastrointestinal tract, but only applied in full in the case of gastritis. In fact, Marshall tested the 3rd Koch postulate,[38] by ingesting a portion of H.p. culture, which caused symptomatic gastritis. In the case of duodenal ulcer, the relationship was established and accepted through proving that cure was associated to eradication of the bacteria.

The association between H.p. and gastric cancer was officially recognised in 1994, when the International Agency for Cancer Research[39] declared H.p. as a type I carcinogen[40] (IARC, 1994). Between 1994 and 2005 guidelines and consensus statements[41] were produced on the role of the H.p as a causal agent in gastric diseases, and on diagnostic procedures and recommendations for screening and treatment according to different situations (Yamada, 1994; European Helicobacter Study Group, 1997; Malfertheiner *et al*., 2002 and 2005).

Helicobacter pylori emerged as an interesting instance of the kind of issues dealt with in science studies, mainly due to the peculiarity of the history of its "discovery" and stabilization, the ways in which it has transformed the understanding of the aetiology of gastric diseases and the worldwide impact of the infection and the variability of its clinical and epidemiological outcomes.

5.2. Overview of Publication Trends

The following analysis focused on bibliographic data collected from Science Citation Index database between 1945 and 2004.[42] This is one of the databases included in ISI - Institute for Scientific Information. It contains online information on 6800 scientific periodicals. The four central terms were searched in the database: campylobacter pylor*, campylobacter gastr*, helicobacter pylor* and helicobacter gastr*. The search was also made for the term "spirochaetes", one of the early terms used to describe micro-organisms found in the human stomach, but the results related mostly to veterinary studies, and it was thus decided to exclude that word.

The four searched terms correspond to the different names given to the bacterium, first believed to belong to the genus *Campylobacter* – a well known genus in bacteriology – and later assigned to a distinct genus, *Helicobacter*. Terms such as pylor* and gastr* allowed a broad range of references to be retrieved.

---

[38] On Koch's postulates, see Chapters 3 and 4.

[39] The International Agency for Research on Cancer (IARC) is part of the World Health Organization. IARC's mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.

[40] Group I carcinogen: carcinogenic to humans.

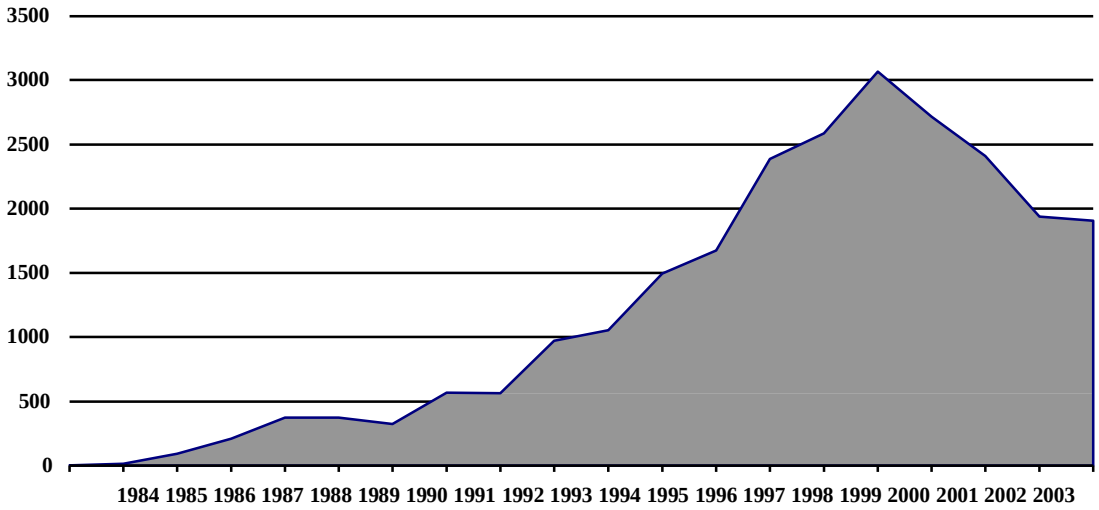
[41] Guidelines and consensus statements are the outcome of international meetings which gathered experts, primary care physicians, and representatives of National Societies of Gastroenterology to establish consensus guidelines on the management of H.p..

[42] The criterion to define the period under analysis was the time span of that database. Although initially the decision was to invest in the analysis of four medical databases – PUBMED, GUT online, SCI, and MEDLINE – some constraints emerged, namely related to the structure of the database for analysis and the available data. After some exploratory work, we came to the conclusion that results using PUBMED were very similar to those obtained through the use of SCI; due to budget constraints, we were not able to access MEDLINE data, which requires the payment of a fee; GUT online data were already included in the SCI. We thus decided that the SCI database would provide the information needed for our study.

Based on these criteria, the search retrieved 24 719 records.[43] These included several types of documents, such as articles (58, 2%); meeting abstracts (24,2%); letters (6,9%); reviews (5,8%); editorial materials (3,2%); notes (1,2%); corrections (0,3%); corrections and additions (0,1%); news items (0,1%) and discussions (0,1%).

In parallel with, and based on the results of bibliometric analysis, cited references of central articles were studied and, when available, full text versions were scrutinized.

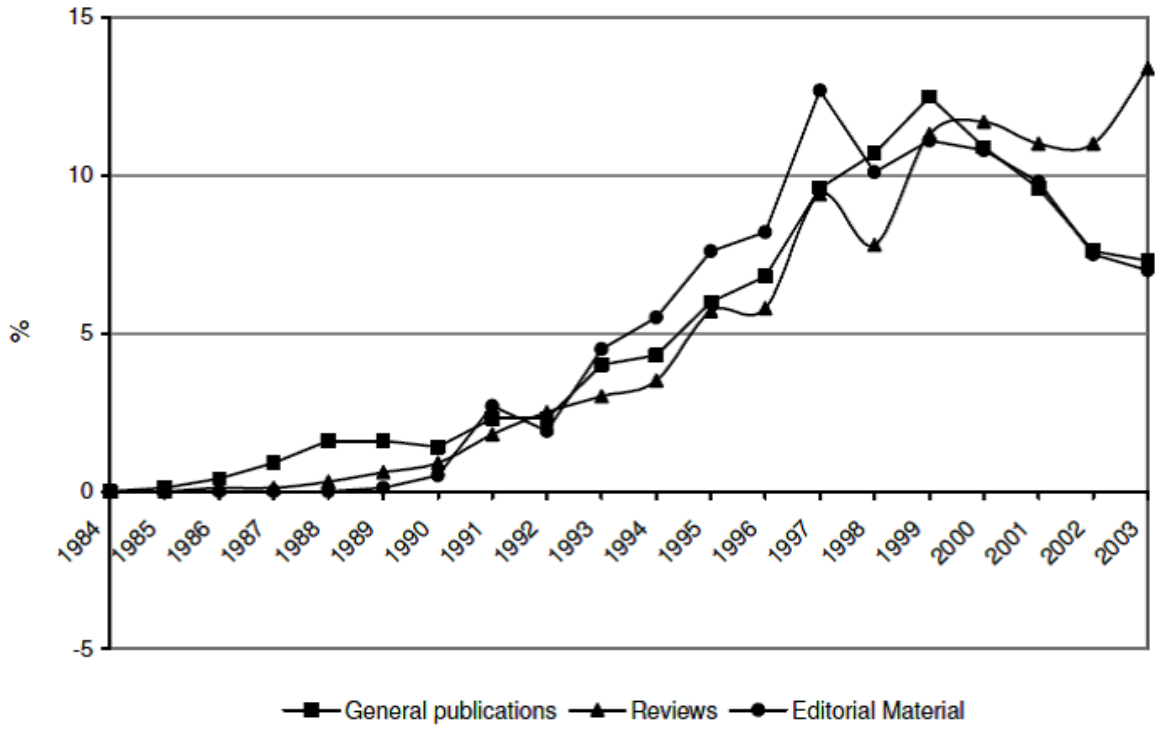
Figure 5.1. Publications number distribution, 1984-2003



The progression of the annual amount of publications on H.p. since the early 1980s provides a first approach to the emergence of a new biomedical object and to the changes in the biomedical world associated with it.

[43] In a first moment, records obtained were "cleaned" in order to eliminate repeated references and to uniform the data. These were then subject to bibliometric analysis using the Bibexcel software, combined with parallel operations using Excel and UCINET software for the construction and analysis of network relations. This software combination was crucial to identify relevant indicators for the reconstruction of the trajectory of H.p. For this report, the analysis was carried out for all types of publications. A separate treatment of two document types – editorial material and reviews – was also carried out, but the results were significant and therefore not included in this report.

Figure 5.2. Evolution of publications number, 1984-2003



Considering the different type of publications under analysis, their evolution curves are very similar to the curve of general publications. Slight disparities, however, can be noticed, and call for some interpretation. In comparative terms, relative to the share of each publication type total, the distribution of publications on H.p. reveal a typical pattern of emergence of a scientific innovation. At the beginning, the *General publications* are of greater relevance. At this time the topic is still new to the community, not being reflected on *Editorial Materials*. These gain importance as the topic becomes consolidated, with a significant growth of *General publications*. This is the case here from 1993 until 1997, the period when *Editorial Materials* are comparatively more significant, recognizing the importance of the topic. *Reviews* have a delayed growth curve, in accordance with its retrospective emphasis, and are comparatively more significant precisely at the time when the other publication types start decreasing, in this case from 2000 onwards.

Notice also that the peak for Editorial Materials is reached in 1997, probably due to the appearance of two major statements related to H.p. management (the 1996 Maastricht Consensus Statement, and the 1997 Updated Sidney System) which may have inspired editorials and similar statements.

5.3. Key Articles, Obligatory Passage Points?

The two first publications on the identification of curved bacilli in the gastric epithelium go back to the two 1983 letters to *Lancet* reporting on Warren's and Marshall's observations of spiral organisms in biopsies of the gastric mucosa. These publications are not included in the last two figures because they do not contain any references to any of the four analysed terms referred above. Instead, they simply refer to *unidentified curved bacilli*. The earliest records found in the search correspond to 3 publications in 1984.

Overall, in both figures it is possible to identify a moderate growth in the number of publications until 1990, corresponding to the reception of and debates over Warren and Marshall's work, and to the consolidation of a new approach to gastric pathologies based on the recognition of the central role of H.p. infection.

Between 1992 and 1999, the growth in number of publications is very significant, bearing witness to the growth of research, but also of controversies over the role and effects of H.p. as a pathogen. It is possible to single out the most cited articles, which presumably were the most influential on subsequent research (only the names of first authors are given):

Table 5.1. Most cited articles

	Most cited articles	Times cited
1	Parsonnet J (1991) "*Helicobacter pylori* infection and the risk of gastric carcinoma **New England Journal of Medicine**	1708
2	Warren J (1983) "Unidentified curved bacilli on gastric epithelium in active chronic gastritis." **Lancet**	1518
3	Marshall B (1984), "Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration." **Lancet**	1438
4	Nomura A (1991) "*Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii" **New England Journal of Medicine**	1053
5	Tomb Jean-F (1997) "The complete genome sequence of the gastric pathogen *Helicobacter pylori*" **Nature**	917
6	Yamada T (1994) "NIH Consensus Conference. *Helicobacter pylori* in peptic ulcer disease. NIH Consensus development Panel on *Helicobacter pylori* in Peptic Ulcer Disease", **JAMA- Journal of The American Medical Association**	846
7	Wotherspoon A (1993) "Regression of primary low grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*" **Lancet**	842
8	Dixon Michael F (1996) "Classification and grading of gastritis: the updated Sydney System" **American Journal of Surgical Pathology**	803
9	Rauws E (1988) "*Campylobacter pyloridis*-associated chronic active antral gastritis". **Gastroenterology**	764
10	Parsonnet J (1994) "*Helicobacter pylori* infection and gastric lymphoma." **New England Journal of Medicine**	747
11	Marshall B (1988) "A prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*." **Lancet**	747
12	Wotherspoon A (1991) "*Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma." **Lancet**	742
13	Forman D (1991) "Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation." **British Medical Journal**	733
14	Graham D (1992) "Effect of treatment of *Helicobacter pylori* on the long-term recurrence of gastric or duodenal ulcer. A randomized, controlled study" **Annal of Internal Medicine**	731
15	Rauws E (1990) "Cure of duodenal ulcer associated with eradication of *Helicobacter pylori* " **Lancet**	719

As would be expected, the 2 nd and the 3 rd most cited items are the two letters to the Editor by Warren and Marshall and the article authored by both published in *Lancet* suggesting a bacterial origin for gastritis.

The most significant number of articles is about the relation between H.p. and common pathologies of the gastroduodenal region, namely gastritis and ulcer. It is worth noticing that whereas Rauws (1990) and Graham (1992) are trying to prove the causal relation between H.p. and duodenal ulcer, almost at the same time Parsonnet, Forman, Nomura (1991) and Wotherspoon (1993) suggest an association between H.p. and gastric cancer. The most cited article explores the links between gastric cancer and infection by H.p.. This would become a central theme in research on H.p..

The 5th article focuses on the first complete sequencing of the genome of a H.p. strain. This anticipates the central role that genetics will come to play especially from the late 1990s onwards on the understanding of the variable virulence of different H.p. strains and on their diverse clinical and epidemiological outcomes.[44] We must also notice the presence of documents of the "guideline" type, which rank 6th and 8th, characteristic of the consolidation of the research on the topic.

A focus on the links established by the most cited articles between the bacteria and some diseases and knowledge fields follows Latour's definition on the existence or reality of scientific objects as a relational property, which depends on the number of significant associations that can be established with other entities (1999: 158). This is the main achievement of the foundational articles of the biography of H.p., which establish or suggest a relationship between the bacterium and gastritis, peptic ulcer disease or gastric cancer. Another instance of this process is the association of the bacterium genetics through the sequencing and genotyping of its different strains. Indeed, each of these associations represents an additional property reinforcing the reality of *Helicobacter pylori* as a biomedical entity.

One of the advantages of this kind of analysis is the possibility to articulate several different indicators so as to make visible relationships which allow relational attributes to emerge. The most published and the most cited authors[45] were thus related in the next table, in order to identify the most prominent members of the thought collective on H.p. (Fleck, 1979/1935).

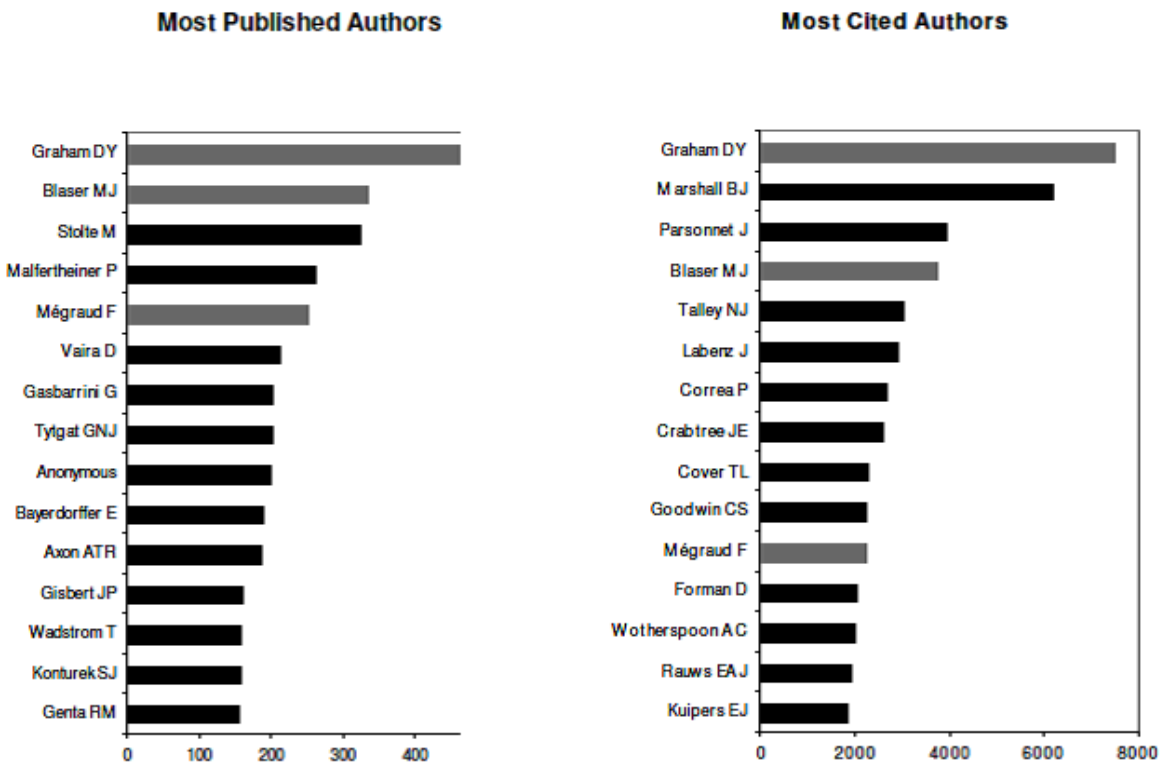
[44] See Chapter 6.

[45] The software used requires that when treating co-authorships only the first name is considered, which means that some authors and co-authorships will be dropped from the analysis.

Table 5.2. Most published authors/institution

Most published authors	Nr.	Institution	Most cited authors	Nr.	Institution
Graham, DY	571	Dep. Medicine Veterans Affaires Medical Centre, Baylor College of Medicine, US	Graham, DY	7521	Dep. Medicine Veterans Affaires Medical Centre, Baylor College of Medicine, US
Blaser, MJ	334	Divison of Infectious Diseases, Vanderbit Univ. School of Med. US	Marshall, B	6211	Royal Perth Hospital, AU
Stolte M	324	Institut Für Pathologie, Klinikum Bayreuth, DE	Parsonnet, J	3945	Dep Medicine Stanford Univ School Medicine, US
Malfertheiner, P	261	Dep. Gastroente, Hepatology and infectiology, Otto von-Guericke Univ., DE	Blaser, MJ	3747	Divison of Infectious Diseases, Vanderbit Univ. School of Med. US
Mégraud, F	253	Dep. Epidemiology and Medical Statistics, London Hosp. Medical College, UK	Talley, J	3045	Dep Medicine Univ. Sidney, Nepean Hospital, AU
Vaira, D	211	First Medical Clinic, S. Orsola Hosp., Univ. Bologna, IT	Labenz, J	2916	Dep Internal Medicine and Gastroente., Elisabeth Hospital, DE
Gasbarrini, G	203	Dep Internal Medicine, Catholic Univ., IT	Correa, P	2685	Dep Pathology Louisiana State Univ. Medical Centre, US
Tytgat, GNJ	202	Dep. Gastroente.- Hepathology, Academic Medical Centre, NL	Crabtree, JE	2608	Division of Medicine St James Univ Hospital, UK
Anonymous authors	199		Cover, TL	2294	Division Gastroente., Univ Hospital Nottingham, UK
Bayerdorffer, E	187	Medical Dep. II, Klinikum, Grosshadern, DE	Goodwin, CS	2245	Dep Microbiology, Royal Perth Hospital, AU
Axon, ATR	184	Centre for Digestive Diseases, general Infirmaryat Leeds, UK	Mégraud, F	2228	Dep. Epidemiology and Medical Statistics, London Hosp. Medical College, UK
Gisbert, J	161	Servicio de Aparato Digestivo, Hosp. Universitario de la Princesa, ES	Forman, D	2063	ICRF Cancer Epidemiology Unit, Radcliffe Infirmary, UK
Wasdröm, T	160	Dep. Infectious Diseases and Medical Microbiology, Lund Univ. Hospital, SE	Wotherspoon, AC	2002	Dep Histopathology, UCL Medical School, UK
Konturek, SJ	160	Institut of Physiology, Medical Academy, PL	Rauws, EAJ	1926	Dep Gastroente., Academic Medical Centre, NL
Genta, RM	155	Dep. Medicine Veterans Affaires Medical Centre, Baylor College of Medicine, US	Kuipers, EJ	1845	Dep Gastroente. and Hemapathology, Erasmus MC-Univ Medical Centre, NL

Figure 5.3. Most published and most cited authors

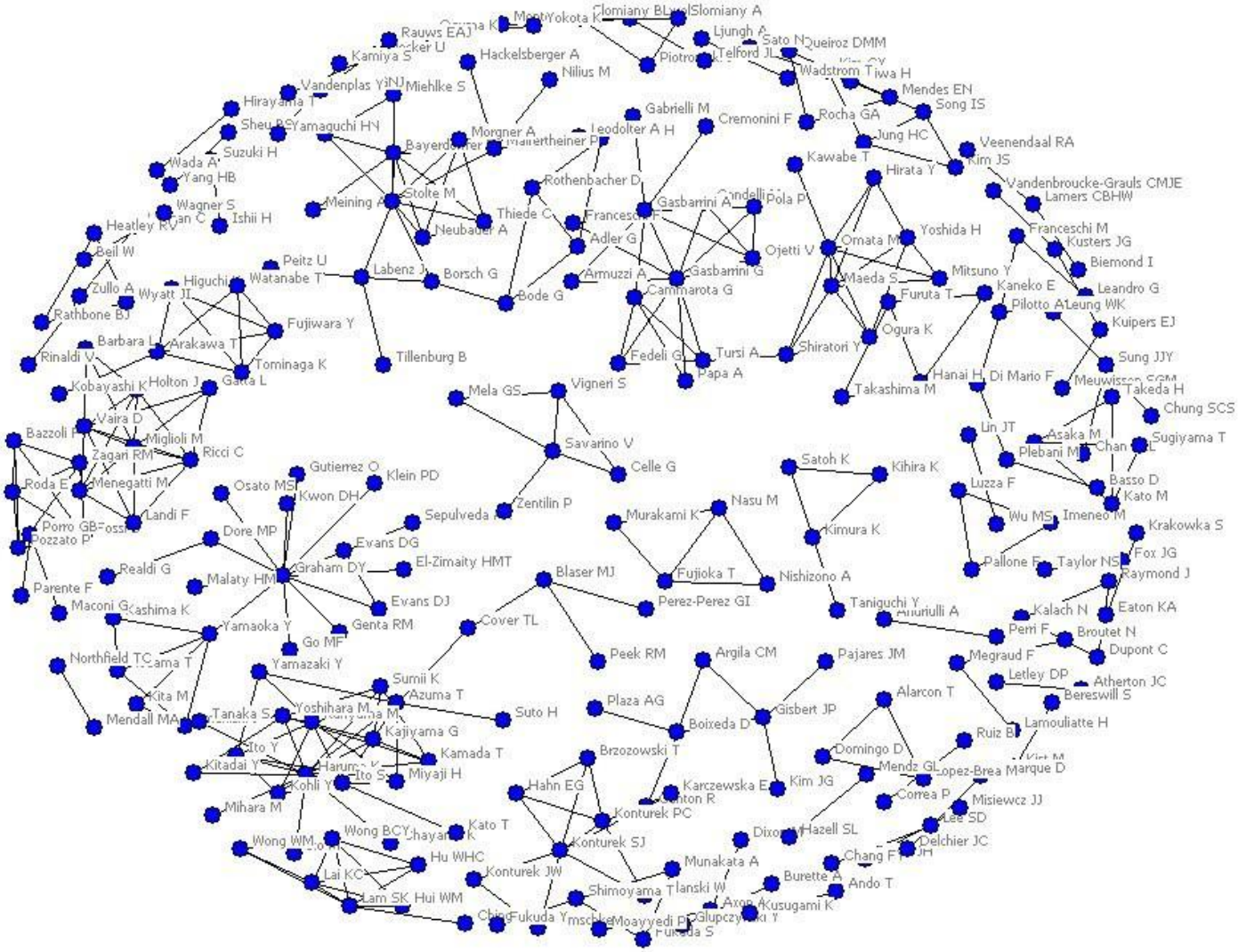


5.4. Building Networks

Social network analysis allows us to observe different features of a network through different measures.

The figure below shows the whole co-authorship network with a density of 4476, meaning that approximately 45% of all possible ties are present.

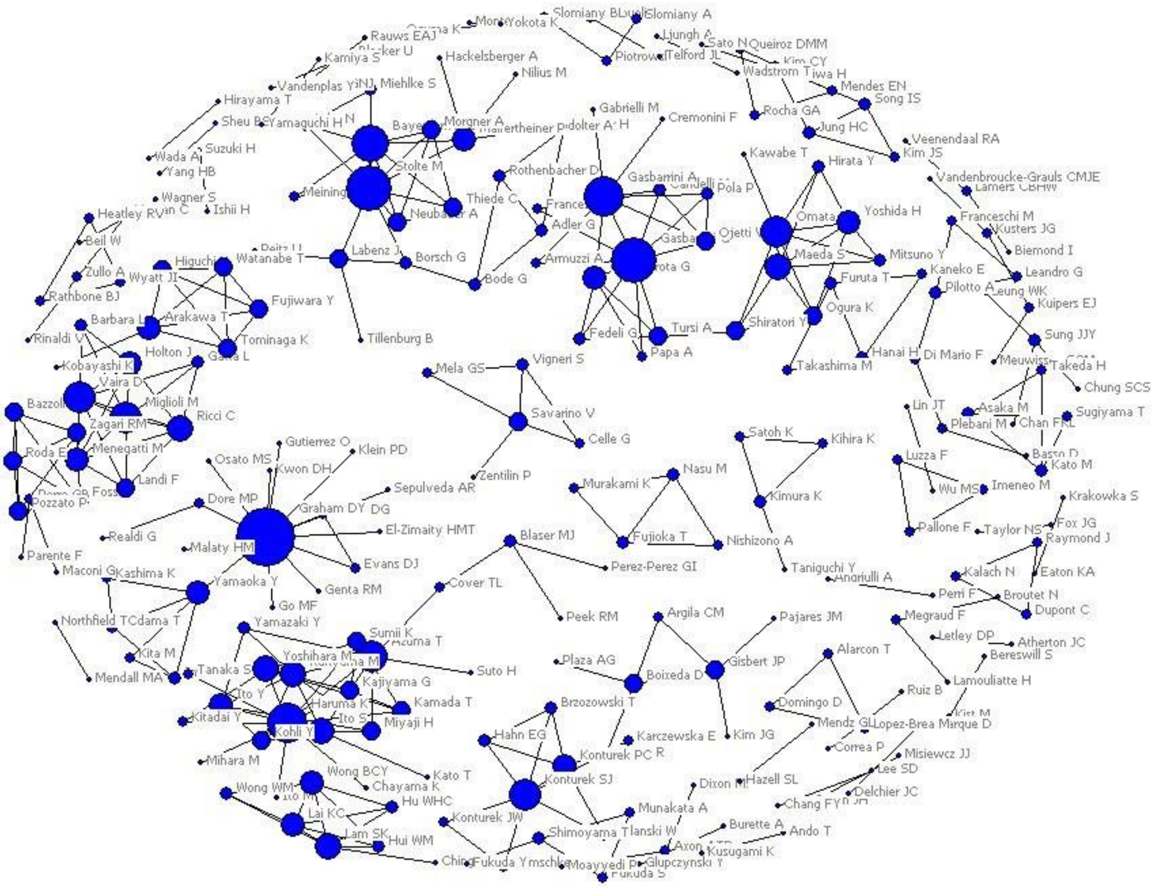
Figure 5.4. Network of co-authorship (1945-2003)



Centrality measures (degree centrality, closeness centrality and betweenness centrality) are among the most relevant. In this analysis we will only consider degree centrality.

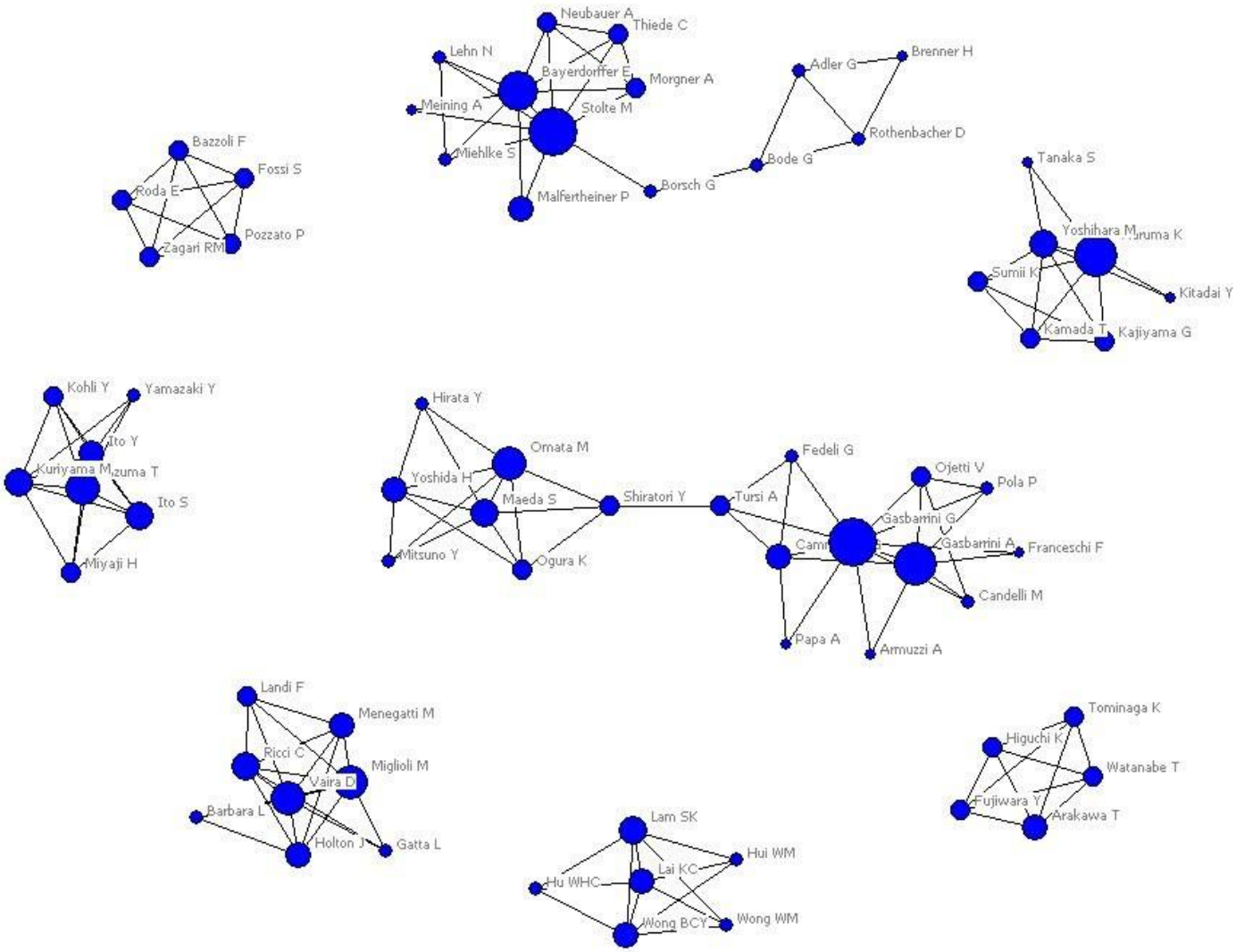
Degree centrality is related to the number of connections of each actor. Actors who have more ties to other actors may be in advantaged positions. Because they have many ties, they may have alternative ways to satisfy needs and are less dependent on other individuals; they may have access to, and be able to call on more of the resources of the network as a whole; and they are often third-parties and deal makers in exchanges among others, and are able to benefit from it.

Figure 5.5. Network configuration - degree centrality



Authors (nodes) with highest values of Freeman degree centrality, i.e. those with a larger number of publications with other authors, are represented with the larger blue circles. The next figure allows a closer observation of the most relevant authors in terms of degree centrality.

Figure 5.6. Co-authorships with highest degree centrality

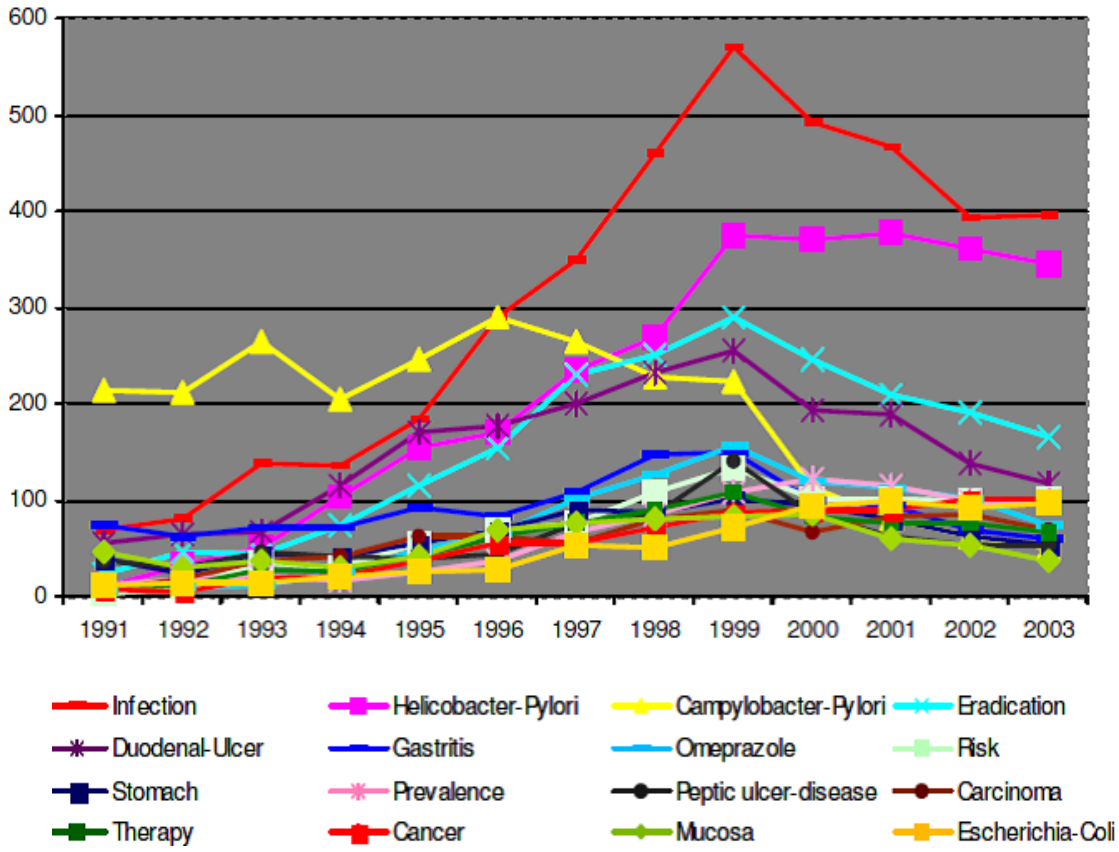


Stolte M, Gasbarrini G, Gasbarrini A, Haruma K and Bayerdorffer E are the authors with more ties in the total network, having more co-authorships. The figure also shows that the most representative co-authorships occur within countries, although Shiratori Y and Tursi A are here connecting Italian and Japanese networks.

5.5. Field Structure

Bibliometric analysis provides other significant indicators, such as keywords. The analysis carried out here uses the terms identified as keywords in the bibliographic reference. In this specific case, the evolution of keywords over time offers a very general picture of the themes which have dominated the field of research on H.p..

Figure 5.7. Key words evolution, 1991-2003



Four keywords emerge from the figure as the most frequent: "infection", "helicobacter pylori", "duodenal-ulcer", and "eradication".[46] The frequency of appearance of the first two should not be surprising, since they refer to an entity and a topic which are common to all publications on H.p. The keyword "infection", in fact, may appear in connection with topics which are not necessarily related to H.p. Thus, their contribution to the analysis is of scarce significance. Other keywords, such as "eradication", are of more significance. In this case, the frequency of this keyword suggests that a considerable amount of publications deal with proposing, testing and evaluating treatment regimens or eradication programs. As a public health concern, eradication is a highly controversial subject, being defined differently and

[46] It must be referred that the database only includes keywords treatment from 1991 on.

argued for, or against, by different authors and actors (States, clinicians, epidemiologists, etc). Interestingly, and despite both assumptions on and evidence of its importance, "eradication" as a keyword has been declining over the last decade. This may be due, paradoxically, to the successful spread of eradication therapies, which are likely to correspond to a growing consensus on their desirability and on their adoption within the community of researchers and clinicians. It may also be the case, as was suggested by some researchers, that the provision of presumably successful, stabilized combinations of drugs for treatment has led to a disengagement of major funding sources, such as the pharmaceutical industry, from supporting new research and thus reducing the encouragement for research and publication. But this may be changing, since the success of eradication treatments is showing a visible decline in some countries, possibly due to the development of resistance to the (or to some of the) antibiotics used for that purpose. It is thus possible that new funding will be injected into research on this topic.

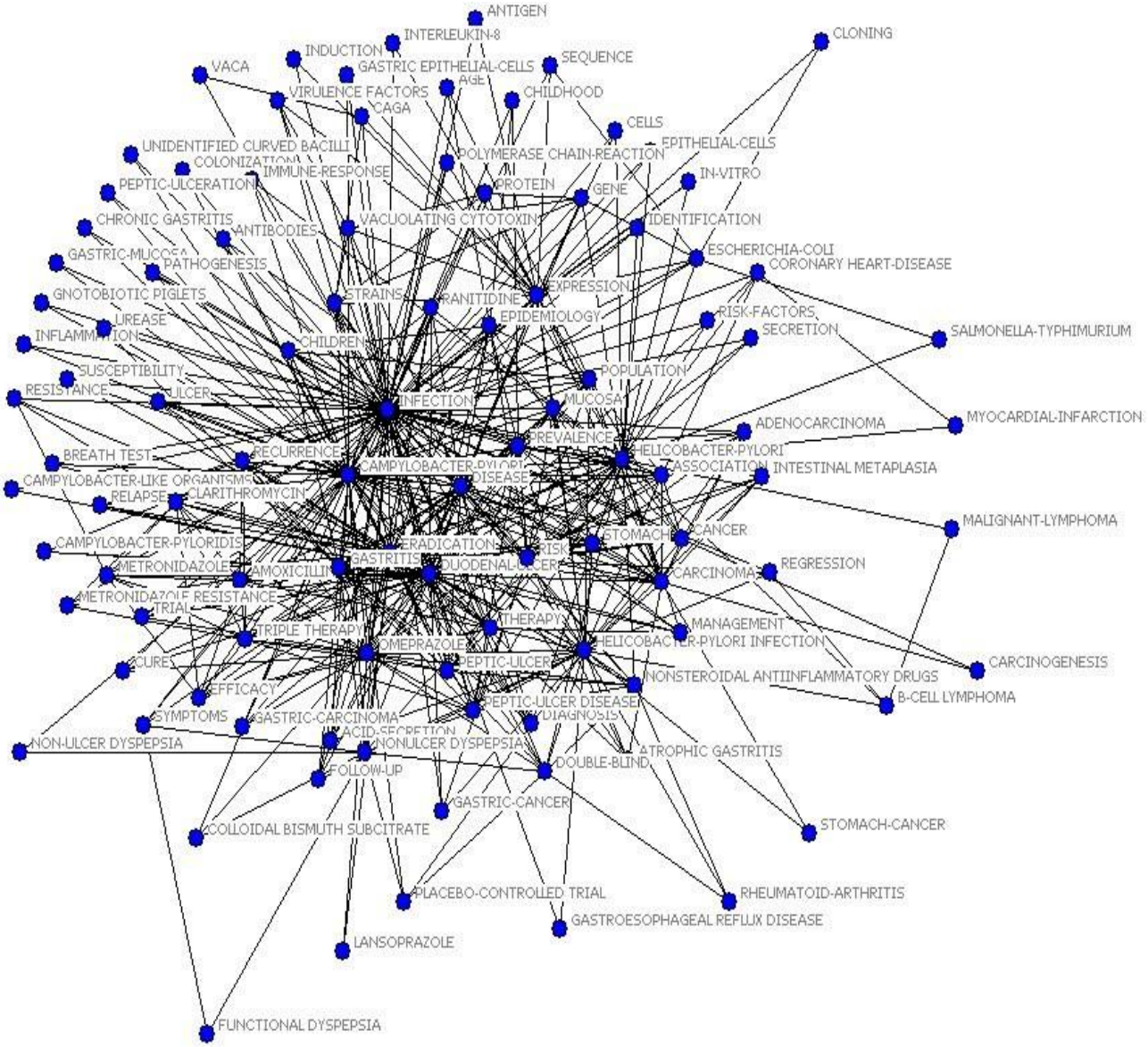
Some keywords such as "risk", "cancer", or "Escherichia-coli" show a tendency to appear more frequently over the last years of the period under analysis. This suggests that themes such as risk factors for gastric cancer associated with H.p. or the association of infection by H.p. with infection by other pathogenic agents may be fueling further research and finding appropriate funding.

Risk appears to be a growing topic, especially regarding its definition and measurement in respect to H.p. infection and a number of pathologies which develop only under circumstances which are still unclear. The only common outcome of H.p. infection in every infected subject who is symptomatic is gastritis. In other cases, sequences of episodes of gastric disease and combination of certain factors (such as host factors, intestinal metaplasia and H.p. infection) may eventually lead to cancer. The contingency and uncertainty of the long-term outcomes of infection are often subsumed under the notion of "risk". The outcomes (gastric cancer, duodenal ulcer) and the numbers of affected people have thus brought the assessment of risks associated with the progression from H.p. infection to these more serious conditions to the attention of gastroenterologists.

Escherichia coli, in turn, is part of the natural flora of the human intestines, where it exists in large numbers. It may have a pathogenic effect when it invades other organs or when strains different from those normally found in the intestine invade the latter. Since *Escherichia coli* was discovered at the end of the 19th Century and has been widely studied, we might take its appearance among the main keywords in this analysis as a sign that research on H.p. may be moving towards a more detailed analysis of the ecology of the gastrointestinal region and of infection of the gastric tract.

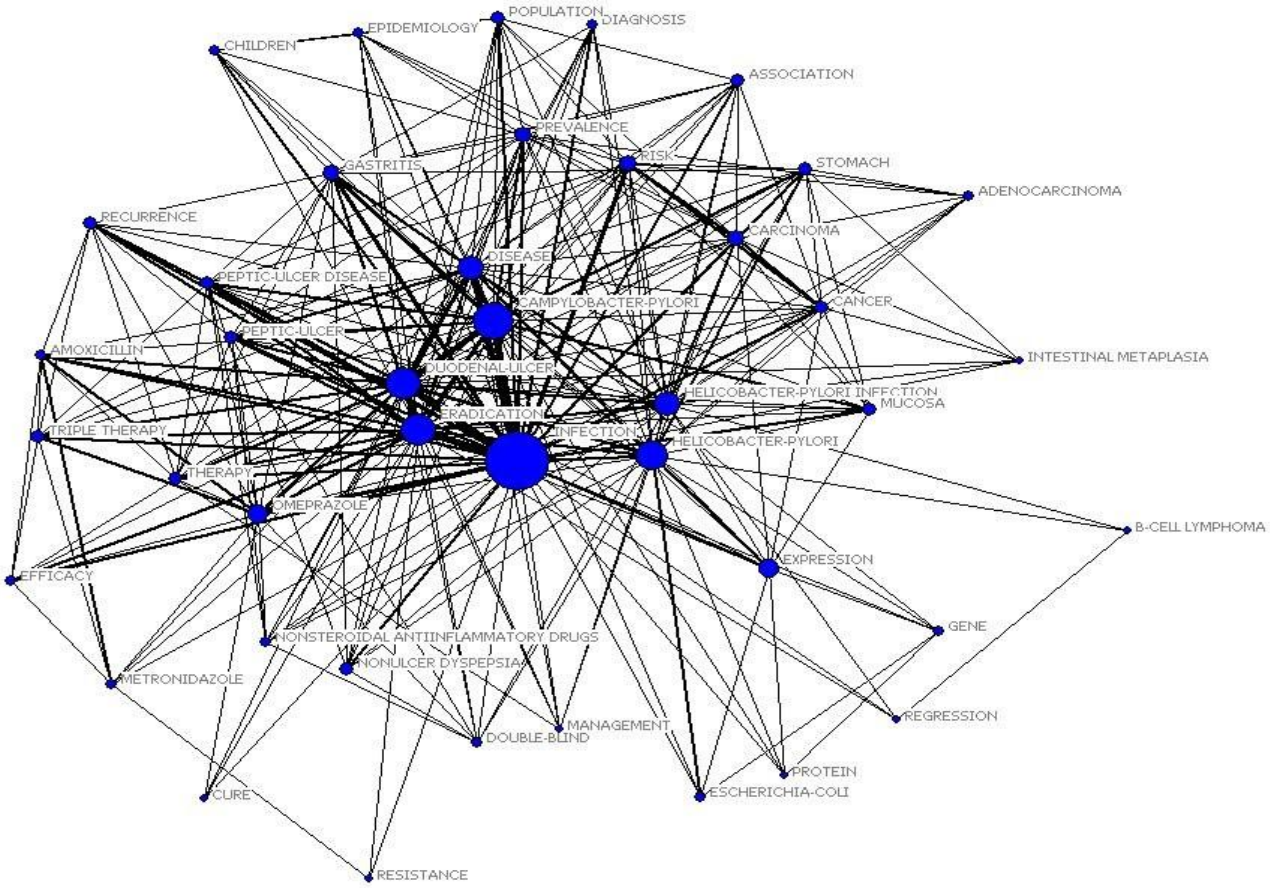
More relevant than the independent keywords for the analysis of the dynamics of the research field is the relation between these, and what it tells us on the relations between different biomedical entities and topics.

Figure 5.8. Network of keywords[47]



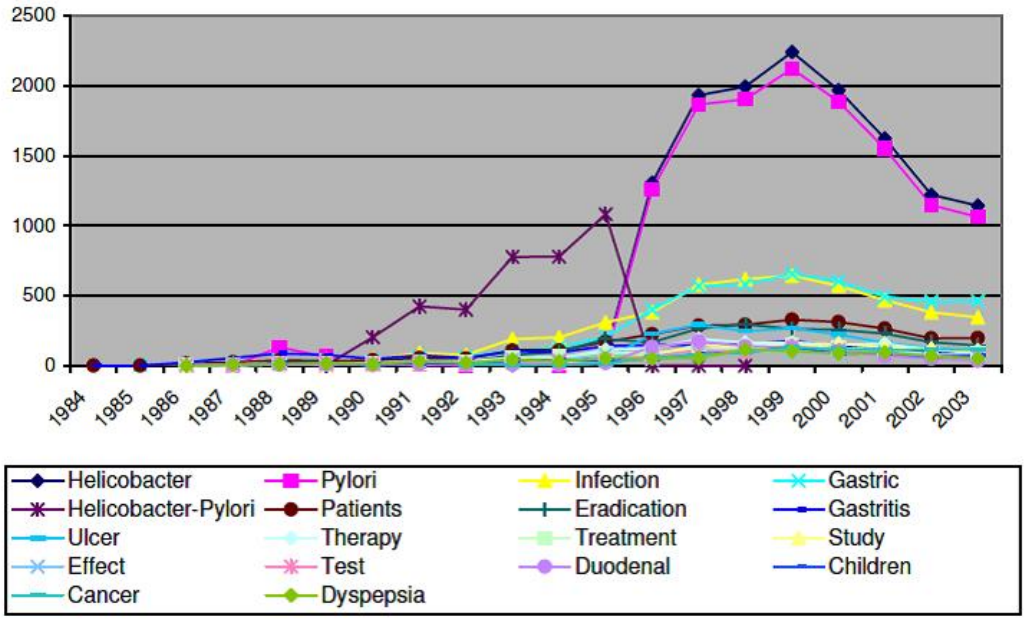
[47] Due to the large volume of data, we include only words with more than 50 co-occurrences.

Figure 5.9. Keywords with highest degree centrality – nucleus (with intensity of ties)



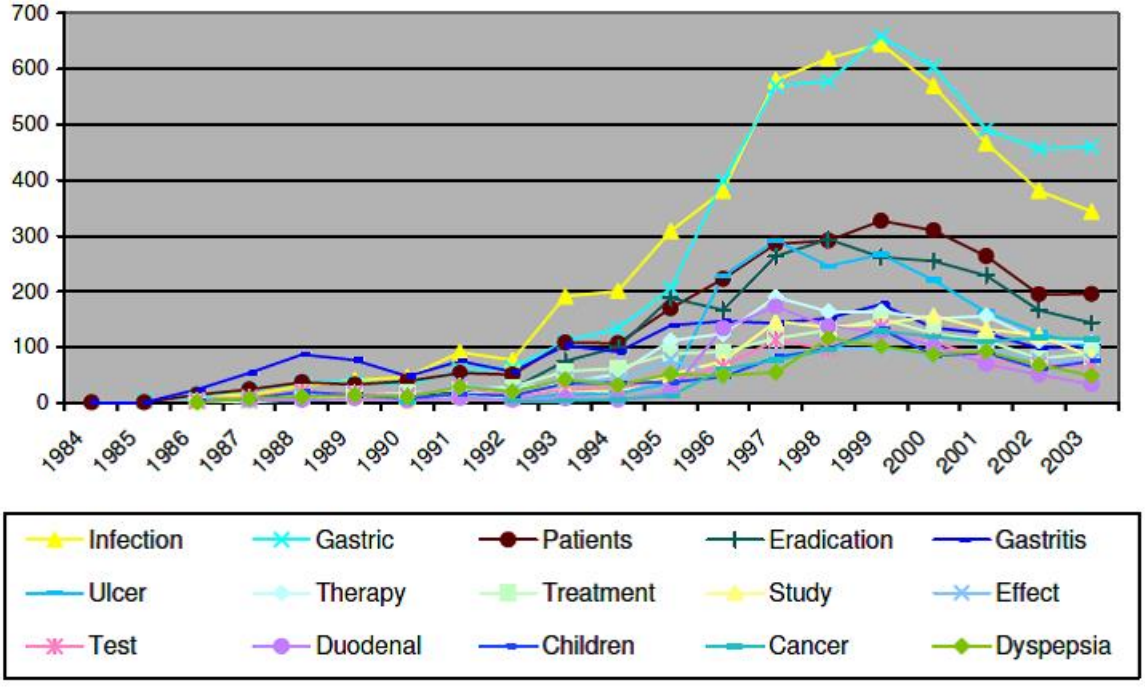
A more detailed representation reveals the keywords with highest degree centrality, such as infection, campylobacter-pylori, duodenal ulcer, eradication, Helicobacter pylori and disease.

Figure 5.10. Words in the title evolution, 1984-2003



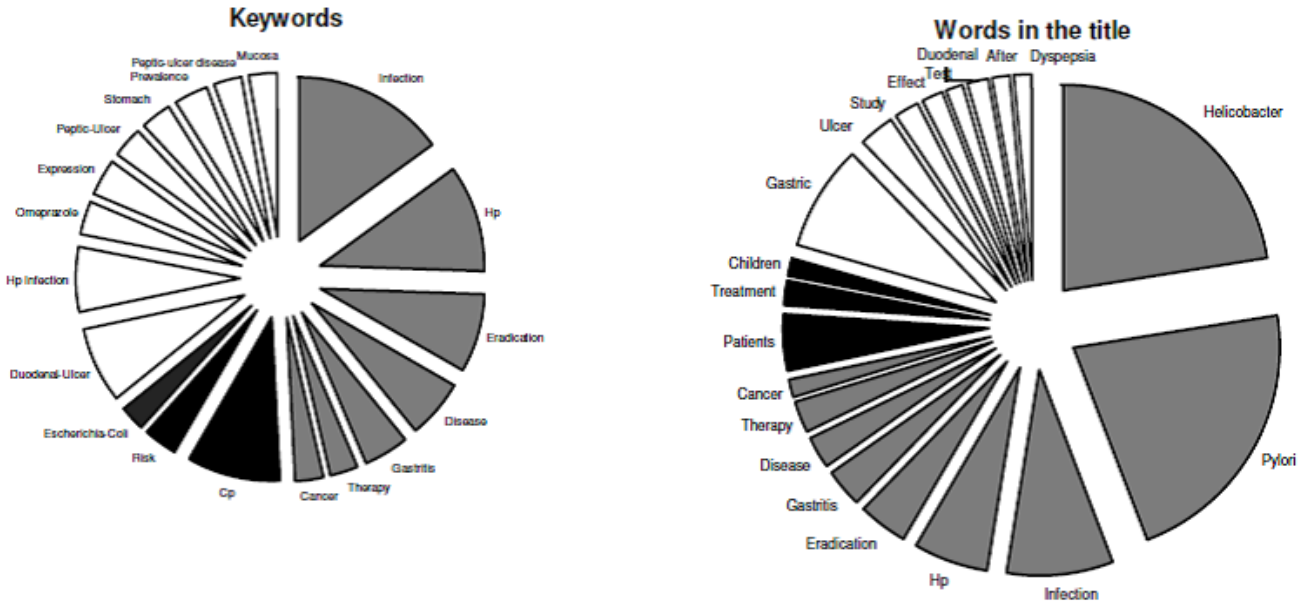
The figure above confirms the diagnosis offered in the previous paragraphs. Not surprisingly, *Helicobacter*, *pylori* and *Helicobacter pylori* are the most frequent words in the titles of publications over the period under analysis.

Figure 5.11. Words in the title evolution, 1984-2003



If we take out *Helicobacter pylori*, *pylori* and *helicobacter* the prominent words in the previous figure, we are able to explore more deeply the relative evolution of the other words. From 1990 onwards, other most frequent words in titles are *infection* and *gastric*, followed by *patients*. This may hint at an increase in clinical research, which would be expected after the initial period characterized by the identification and description of the new pathogen and the demonstration of its association with gastritis. By 1990, treatment was already available, and the assessment of its success was a major concern of the H.p. community.

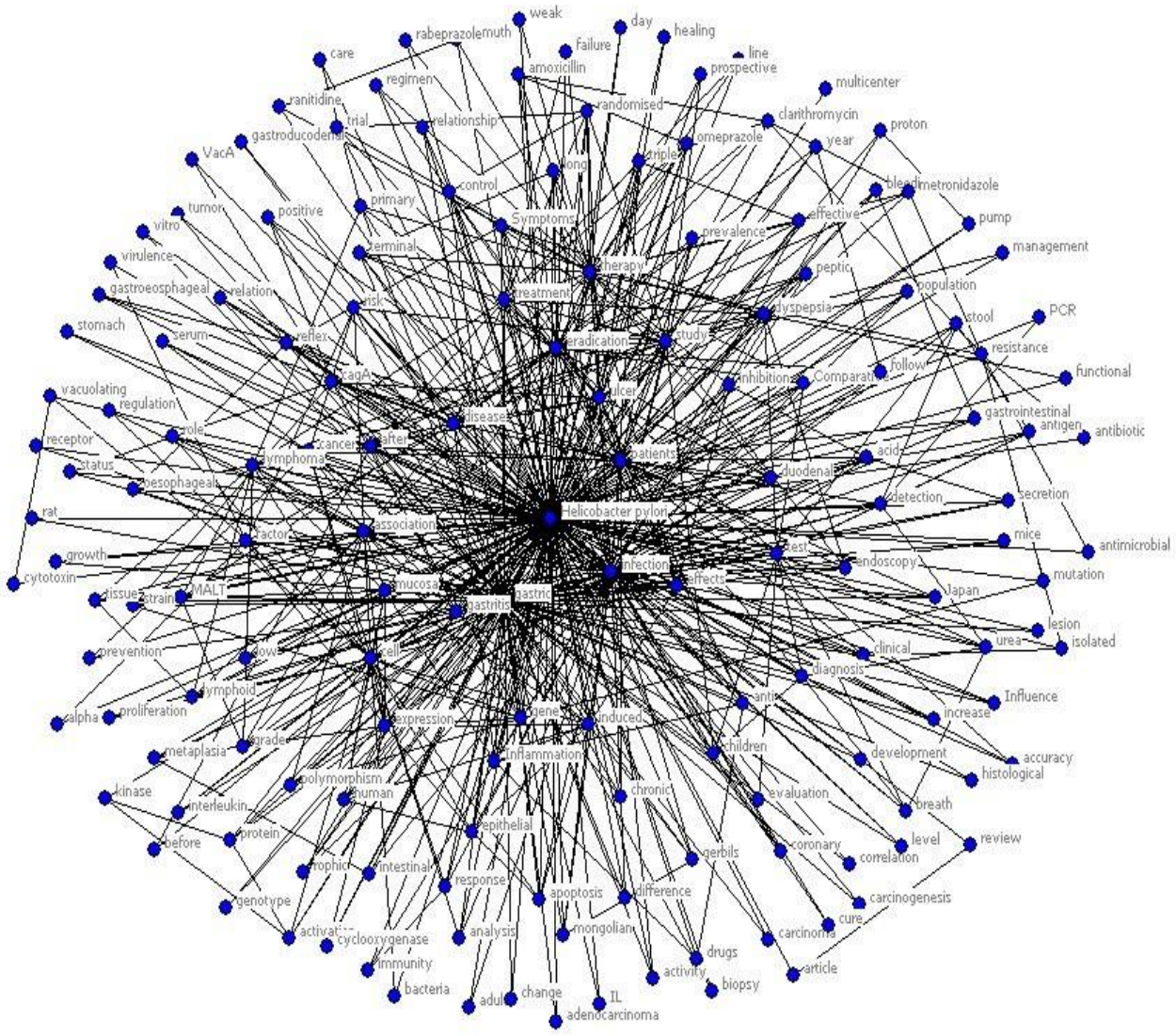
Figura 5.12. Keywords and words in the title comparision



Legend: Grey- Common words across the two figures; **White**- Specific words relevant to Hp; **Black** - Other words

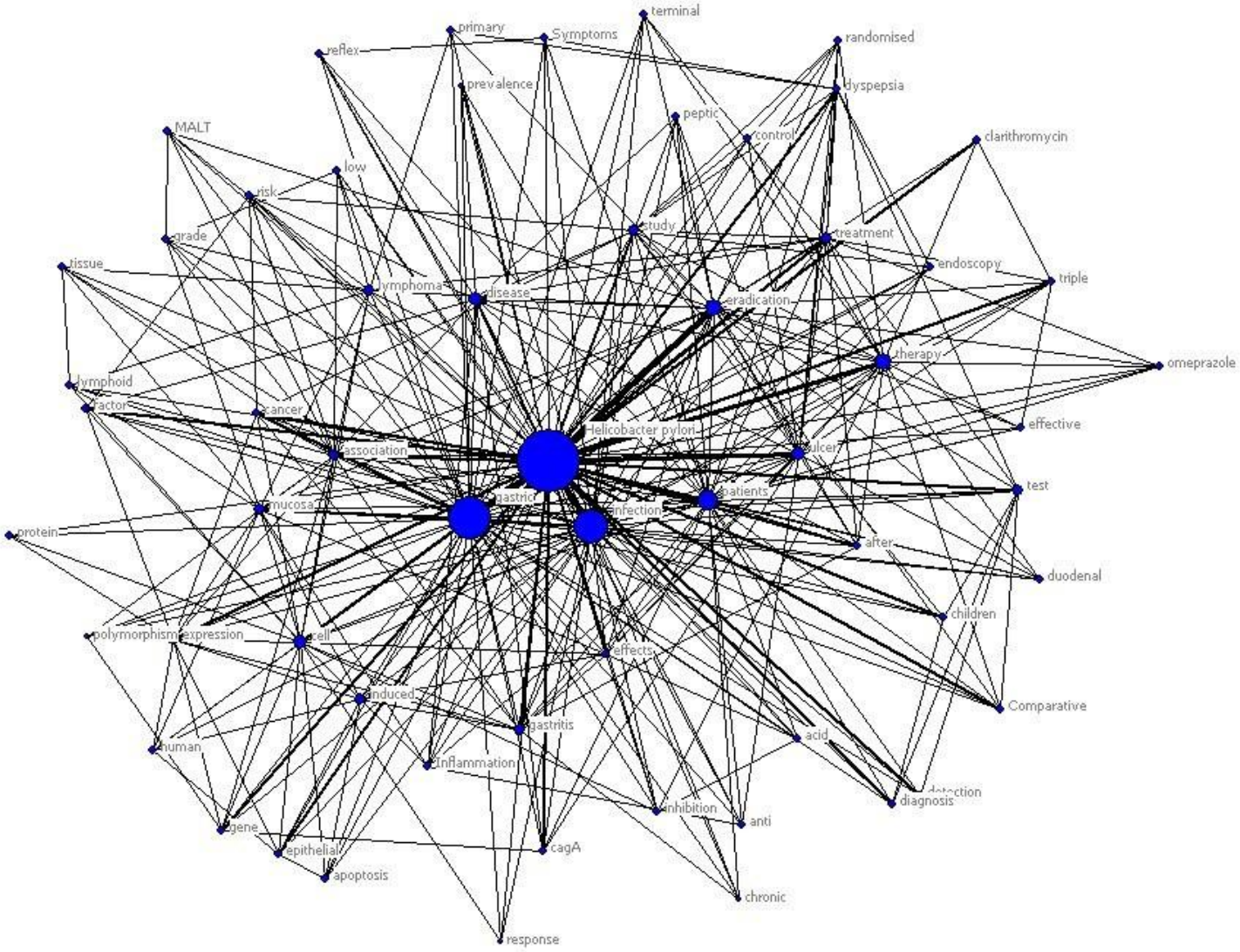
Two features are noticeable in these figures. On the one hand, and not surprisingly, many of the words are common to both the titles and keywords of the publications. On the other hand, some words appear only in one of the figures. Words like *treatment*, *patients* and *children* only appear in titles. This stems from the fact that they are not field specific, and thus do not carry the identification weight of keywords. But it may also hint at the type of journal the articles are published in, the type of research reported on and the kind of public the publications in question are addressing. In this case, they are both likely to be authored by and addressed to clinicians or clinical researchers. The history of H.p. is thus a history of a diversification of research topics and styles, exploring different directions and addressing different publics, including biomedical researchers, clinicians, pathologists, microbiologists or geneticists. This diversity is itself a marker of the changing identities attributed to H.p., of its variable ontology, as we have called it elsewhere. An interesting indicator of this diversity is the growth in the diversity of journals hosting articles on H.p. from 1984 to 2003.

Figure 5.13. Network of words in the title[48]



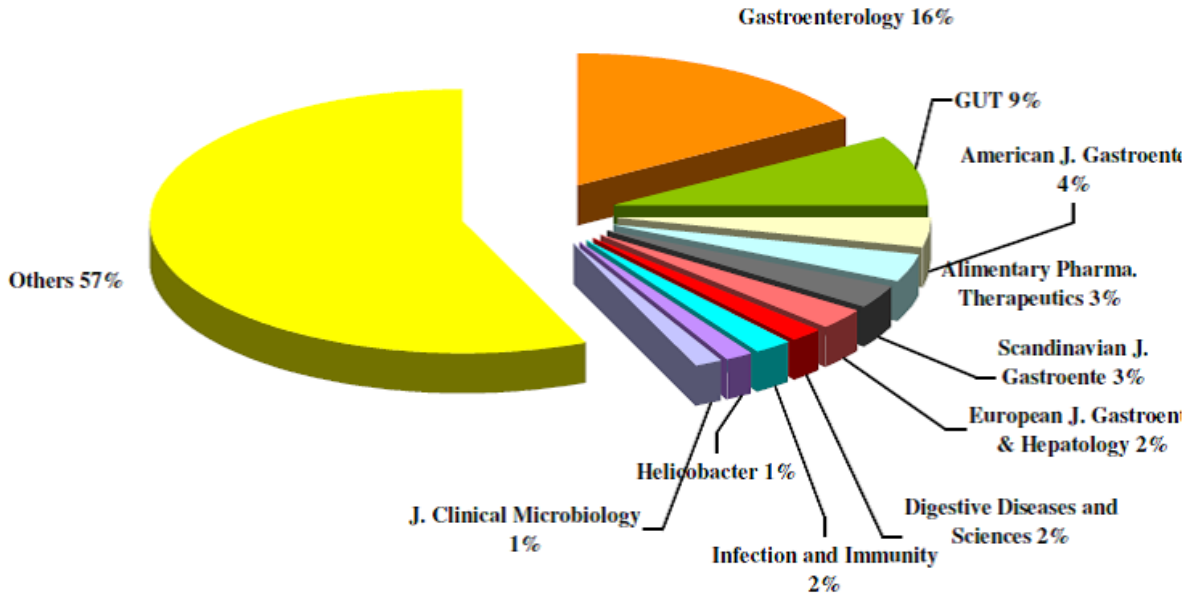
[48] Due to the large volume of data, we include only words with more than 25 of co-occurrences.

Figure 5.14. Words with highest degree centrality – nucleus (with intensity of ties)



Not surprisingly, *Helicobacter pylori*, *gastric* and *infection* are the core of words in the title, more frequently connected with other words. A second line of words, like eradication, therapy, ulcer, patients, effects, gastritis, inflammation, induced, cell, mucosa, association, cancer, lymphoma, disease and study, are also important to highlight in this context. Comparatively to the analysis of keywords, the variability of words is much smaller.

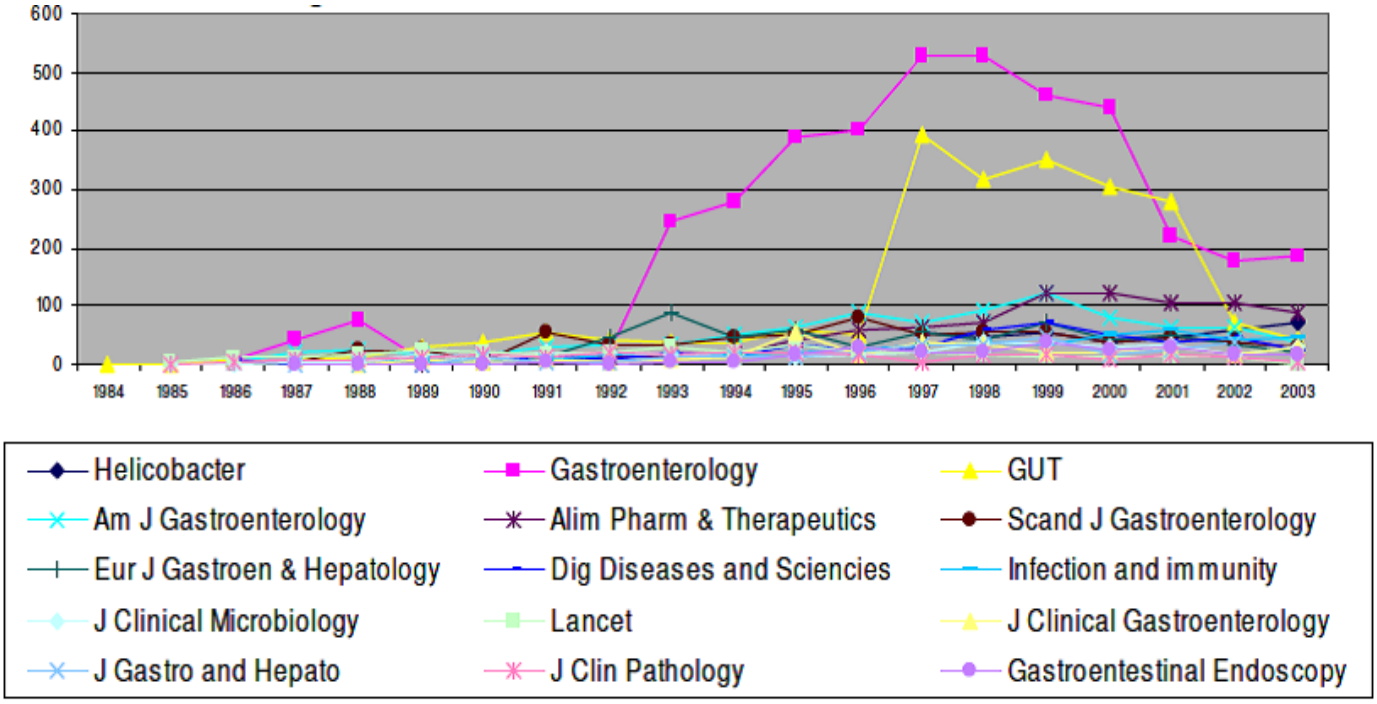
Figure 5.15. Publications per Journal



The major outlets for publication are journals associated with the biomedical specialty of gastroenterology, or with the biology and pathology of the human gastric tract, such as *Gastroenterology*, *GUT*, *American Journal of Gastroenterology*, *Scandinavian Journal of Gastroenterology*, *Digestive Diseases* and *Sciences* or *Hepatology*. Other significant outlets are journals aimed at publics broader than the community associated with H.p., such as *Alimentary Pharmacology and Therapeutics*, *Infection and Immunity or Journal of Clinical Microbiology*, *The journal Helicobacter*, which is sponsored by the European Helicobacter Study Group, is the only publication specifically devoted to research on H.p.. All the publications mentioned host at least 1% of the total publications on H.p. identified in our database. Two journals (*Gastroenterology* and *GUT*) concentrate 25% of the publications, 10 journals gather 43%. The remaining 57% of publications are spread over 1513 journals, covering a wide range of disciplines and specialties. Indeed, the relevance of the bacterium as an object of different disciplines and specialties is a persistent feature of its trajectory. It is worth noticing that the early articles establishing the existence of the bacterium were published in generalist medical journals, such as *The Lancet* or *The New England Journal of Medicine*, and not in gastroenterology journals.

Indeed, the relevance of the bacterium as an object of different disciplines and specialties is a persistent feature of its trajectory. It is worth noticing that the early articles establishing the existence of the bacterium were published in generalist medical journals, such as *The Lancet* or *The New England Journal of Medicine*, and not in gastroenterology journals.

Figure 5.16. Publication Source Evolution 1984-2003



As shown in the previous figure, a longitudinal depiction of the publication sources on H.p., a diverse range of sources publishes on topics related to H.p.. It should be noticed, though, that over the period 1992-2001 two journals appear as a popular locus of publication on H.p, even though the number of articles published on these topics has shown a tendency to decline over the early years of the present decade. The period 1994-1997 is central for the history of H.p., due to the publication of the first guidelines and also of the Updated Sydney System for Classification and Grading of Gastritis, which may explain the peaks in the figures.

Figure 5.17. Most cited Journals

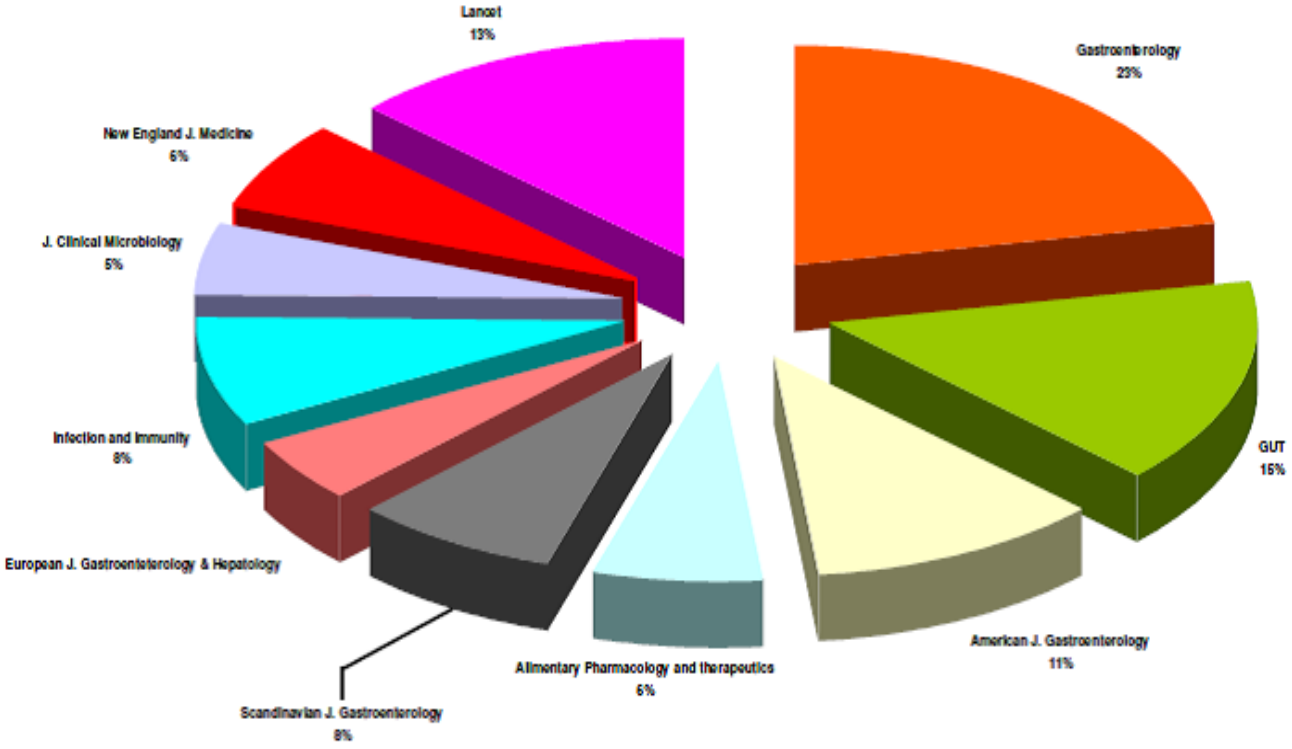
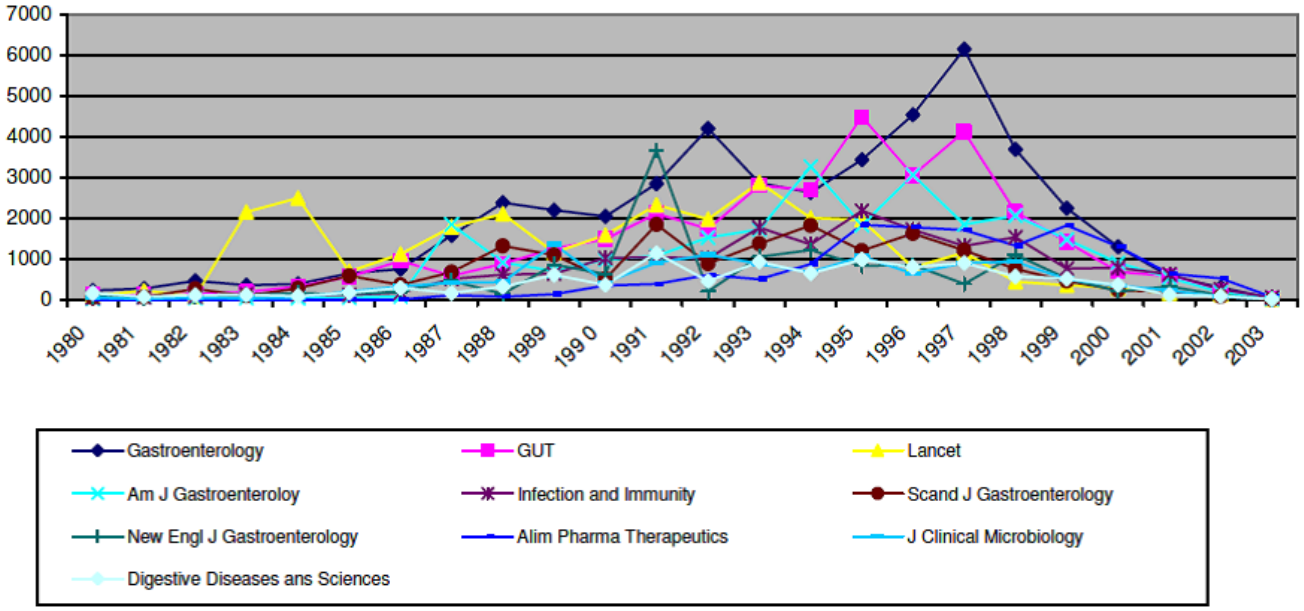


Figure 5.18. Cited Journals along the period 1980-2003



A longitudinal analysis of the cited journals, according to the year of the original cited publication, provides an interesting picture, sensitive to some of the central episodes of the history of H.p.[49] Between 1982 and 1985, *The Lancet* appears as the most cited journal. This is easily explained by the publication of the early accounts of the identification of curved bacilli in the stomach by Warren and Marshall in 1983 and 1984. In 1991, the *New England Journal of Medicine* becomes the most cited journal, thanks to Parsonnet's article on the relation between H.p. infection and gastric cancer, as well as Nomura's article, in the same year, on the same subject. These articles, as we saw before, were two of the most cited articles on H.p. (the first and fourth in the ranking). From 1988 on, *Gastroenterology* rises to a prominent place in the citation ranking for the periods 1991-1993 and 1995-1998. GUT increases its presence in 1993-1997. The central role played by these two journals from the 1990's on may be the expression of a situation where the existence and pathogenic role of H.p. have become an established scientific fact, but the subsequent definition of guidelines for diagnosis and treatment are still under discussion. It should be recalled that the main documents establishing guidelines for diagnosis, management and treatment of H.p. infection were issued during that decade: the 1994 NIH Consensus Statement, the Maastricht Consensus Statement (1997) and the Update Sydney System (1996). While in the initial period new associations were still being developed, and as such results were published in a more dispersed way, in the later period a more specific research agenda and research community developed, focusing on a more narrow number of journals, specific to the field.

5.6. Geographical Distribution of H.p. (research)

The prevalence of H.p. infection is variable across different countries and regions of the world. Japan, China and most of South-East Asia, the African Continent, Latin America and Southern Europe are among the most affected regions.

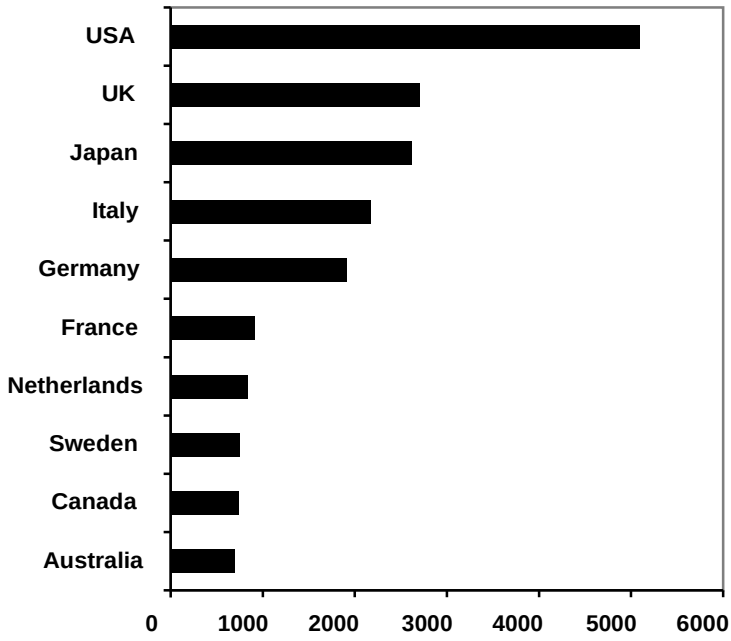
5.19. Geographical distribution of H.p. prevalence

Source: elfstrom.com/arthritis/ nsaids/ulcers.html

[49] It should be noted that the total number of citations are being considered here, and not a moving citation window. This is because this study, rather than focusing on evaluation purposes, for which a moving 4-year window would be recommended, focuses on mapping the field, and as such it was decided to use all available data, rather than restrict this. As such, the more recent publications have a smaller citation period, which explains the decrease in total citations in the most recent years.

The literature brings to the fore the varying infection rates and their geographic distribution. The map above, displaying the situation in 1997, provides a rough picture of this diversity and of the global significance of infection by H.p..

Figure 5.20. Publications per country (all authors included)



A comparison of the map with the figure above, however, displays the lack of correspondence between the prevalence of infection by H.p. and the amount of research carried out, as measured by the number of publications, in different parts of the world. As is true of most scientific areas, including biomedicine, the most productive countries are not those whose population is most affected by the conditions or problems of interest. This picture, however, may be changing, mainly due to the increasing involvement of researchers coming from countries where H.p. infection is a problem. This is confirmed by Adrian Lee, referring to the changing composition of participants in the Annual Workshops of the European Helicobacter Study Group:

> …there's been funding in Europe, America, UK and just a bit Australia, so I just think there might be interest but there wasn't the money to bring it across (…) now there are more and more people from the countries where actually it's a major problem (Interview).

It would be of great interest to determine, for each country, the proportion of publications related to H.p. as a proportion of total biomedical publications. This could be used as a rough proxy for the weight of research on H.p. in biomedical research. Unfortunately, current data do not allow this kind of exercise to be carried out.

An interesting case is that of Japan. It figures among the most productive countries and it has displayed very high rates of H.p. infection and gastric cancer. In this country, H.p. infection was considered a public health problem, justifying a very extensive national eradication programme. This is not the case of Portugal, in spite of its status as one of the most infected countries in Europe (more than 80% of the population infected), as well as a decreasing but high rate of gastric cancer. Portuguese researchers have been making significant contributions to the field, and they have been active in advising public authorities to consider H.p. infection as a public health issue, though with no significant results.

The described results do not have the pretension of representing the whole of publications on H.p., being limited by the reach of the SCI database. Nonetheless, we may consider that they give us a very good general picture of the research on H.p. since 1945 to 2003. The analysis of publications on H.p. is only one way to study its historicity, which is built by different relations established between the participants of a whole network, including H.p. itself, researchers, physicians, politicians, patients, other bacteria, diseases, publications…

As Daston (2000) refers, there are four approaches to the historicity of scientific objects: salience; emergence; productivity and embeddedness. Bibliometric analysis has allowed us to tackle emergence and productivity in relation to H.p. history. Objects emerge as scientific when they appear in a given moment without having any daily pre-history. Although we know some of the ideas, studies and experiences that, before 1983, pointed to the existence of micro-organisms in the stomach, at that time H.p. did not exist for science, and as the results in the database show, it becomes reported only from 1984 on.

Productivity, in turn, is a prominent feature of H.p., since over time the latter becomes associated with more biomedical entities (pathologies, micro-organisms like Escherichia-coli, genes…), it raises new questions as in the debate about eradication and public health, the mechanisms of carcinogenesis, or what pathogen and host genetics have to say about different outcomes of the infection by the same organism. It is also a very important contributor to the defying new ways of approaching health issues, such as risk and non linear causality (Cicolella and Browaeys, 2005).

The more associations a scientific object establishes with other entities the more real it becomes (Latour, 1999). This opens, of course, the possibility of the opposite movement: losing in reality. In fact, H.p. infection presents a decreasing tendency in Western countries, as well as the diseases related to it (Graham, 2006). This is even one of the arguments presented against generalised eradication programs. Can this be related with the decrease of the number of publications on H.p.?

Some H.p. researchers interviewed mentioned that peptic ulcers caused by H.p. are no longer a problem, as they have been understood and effective therapy is available. In their view this explains, in part, the decrease of publications in the last few years. Drug companies, a central source for research funding, are no longer investing in H.p. research since they also consider the problem to be solved. However H.p. researchers claim additional funding in areas such as antibiotic resistance, vaccination, cancer prevention and treatment.

> The reality is that the ulcer story, to some extent, is sorted and finished. There's a lot of work to be done on issues of this ever ending thing about treatment. (…) drug companies are basically not giving money anymore, as far as they are concerned the problem is solved, because they are not bothered about gastric cancer, they have all pulled out because they figure they have made their billions and now there is no more money to be made." (Adrian Lee) "There's a lot of work to be done on issues of this ever ending thing

> about treatment, but, but, where it goes is, people finally get to gastric cancer actually it has become an end point in terms of evidence (…). (C. O'Morain)

This does not mean that H.p. is irrelevant as a health problem. Indeed, gastric cancer still presents high rates in some parts of the world and some authors point out that about 50% of the world population is infected with H.p. (Parker, 2004: 304). Researchers point out that gastric cancer is the current main theme in H.p. research.

> There are a lot of later lessons still to be learned there, but the big one is gastric cancer, still number three killing cancer in the world (…)" (Adrian Lee) "(…) and the big new development in public health issue is gastric cancer. (O'Morain)

The European Helicobacter Study Group – EHSG

Scientometrics also provided the tools to analyse available information on what is presently the most important international collaboration for research on *Helicobacter pylori*, the European Helicobacter Study Group (EHSG). We have analysed the configuration of themes on which the activity of the group has been focused, as well as the composition of the collaborative networks which have coalesced within the Group.[50]

We have used mainly data provide by EHSG on their annual workshops, which have been taking place since 1988. Both the bulk of the data and our constraints of time and resources allowed us only, at this stage, to work on a particular set of the data. We expect to broaden the analysis in the near future and to make fuller use of the data base. The data cover the period 1998 – 2005.[51] In order to construct most of the indicators we used, we "cleaned" the raw data and standardized them into Excel matrices. We then analysed them using two different types of software, Bibexcel and UCINET, following the same procedures used for the analysis of the data collected through the SCI database.

About the European Helicobacter Study Group

The European Helicobacter Study Group (EHSG) is a multidisciplinary group, registered in France as non-profit organization, composed of one representative from most of the countries of the European Union – Denmark, UK, Italy, Austria, Netherlands, Portugal, Germany, France, Ireland, Spain, Greece, Finland, Sweden – plus one representative from Switzerland. The Group also includes four emeritus members, four honorary members – Barry Marshall being one of them - and corresponding fellows in India, Brazil, Japan, Korea, Thailand, Israel and China. It was founded in October 1987 in Copenhagen, Denmark, but according to Francis Mégraud, currently the secretary of the EHSG, its history dates back to 1982-3, when researchers were gathering around the new organism after it was presented at the Campylobacter conference in Brussels (F. Mégraud, interview). Between 1983 and 1987, researchers set up collaborations involving mostly those coming from Northern countries, organizing small meetings in Germany and Denmark (Copenhagen), with 25 to 30 participants from several European countries and one researcher from the USA. Since 1988, the EHSG

---

[50] A first approach to the evolution of *Helicobacter pylori* research in the frame of this group was presented by Francis Mégraud (2007).

[51] The 2006 data were also available, but because indispensable information on co-authorships was missing, we decided not to consider that year.

organizes an International Workshop, every year in a different location in Europe. The earlier workshops included training courses on laboratory techniques, diagnostic methods, epidemiology, clinical trials. In the early 1990s, members from Ireland, Italy, Portugal and several Eastern European countries were invited to join the group, and the number of countries represented started to grow. In its early years, the group had a rather informal organization. It was formalized as an association in 1997, in France. The main physical basis for its activities, however, is located at the University of Vienna, Austria.

EHSG was also the promoter of meetings with the purpose of producing consensus statements/guidelines for the management and treatment of *Helicobacter pylori* related diseases. To this date it has delivered three consensus statements: the *Maastricht Consensus Report* (1997), *Maastricht 2-2000 Consensus Report*, and the *Maastricht 3-2005 Consensus Report*. It 1998, it also jointly organized the meeting which delivered *Helicobacter pylori* Infection in Children: A *Consensus Statement with the Helicobacter pylori Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition*. According to C. O'Morain (interview), EHSG was the first group to produce guidelines, later followed by other in USA and Canada.

EHSG publishes the proceedings of its Annual Workshops and organizes symposia during the European Congresses of Clinical Microbiology and the United European Gastroenterology Weeks. From 1994 to 2001, the Group was responsible for the publication of a special issue of *Current Opinion in Gastroenterology* entitled *The Year in Helicobacter pylori*, now Year in Helicobacter 2002, 2003, 2004, 2005, 2006.

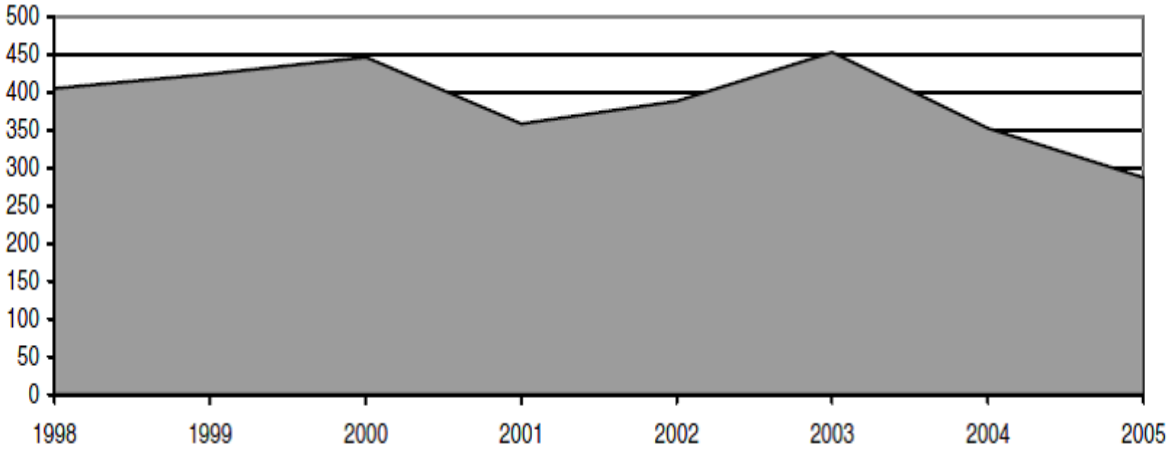
In the past, ESHG has organized studies to evaluate serological kits and to standardize antibiotic susceptibility testing in collaboration with other scientists. It participated in a Biomd project (Eurohepygast) and organized a working group to publish *Guidelines for Clinical Trials for Eradication of Helicobacter pylori*. Technical courses were organized in 1994, 1995, 1996 and 1998. The Group is currently developing a project for the exchange of sera in which researchers from the Department of Microbiology and Hygiene, University Hospital of Freiburg, Germany, and the Departments of Clinical Microbiology of the Rigshospitalet, Copenhagen, Denmark, and the University Hospital of Lund, Sweden, have developed immunoblot diagnostics for *Helicobacter pylori* based on well characterised cell surface antigens, which are then evaluated by other laboratories.

Pharmaceutical industries had a major role in funding the activities of the Group, particularly between 1996 and 2001, a time during which, according to Mégraud (interview), the companies showed interest in this subject. Nevertheless, EHSG activities are still partially supported by grants from AstraZeneca, AxcanPharma and Altana Pharma.

The EHSG has mostly functioned as something like a club, rather than a traditional scientific society (F. Mégraud, interview). In the early years, the Group was eager to attract people with different backgrounds and different research interests. Over time, and according to Mégraud, dispersion has increased, and communication between clinicians and basic researchers has become more difficult. Mégraud also interprets a relative decrease in the attendance of the Annual Workshops as probably due to the very success of early research: the problems that had been at their origin seem to have been solved. Among the current concerns of the Group, gastric cancer appears as the main one.

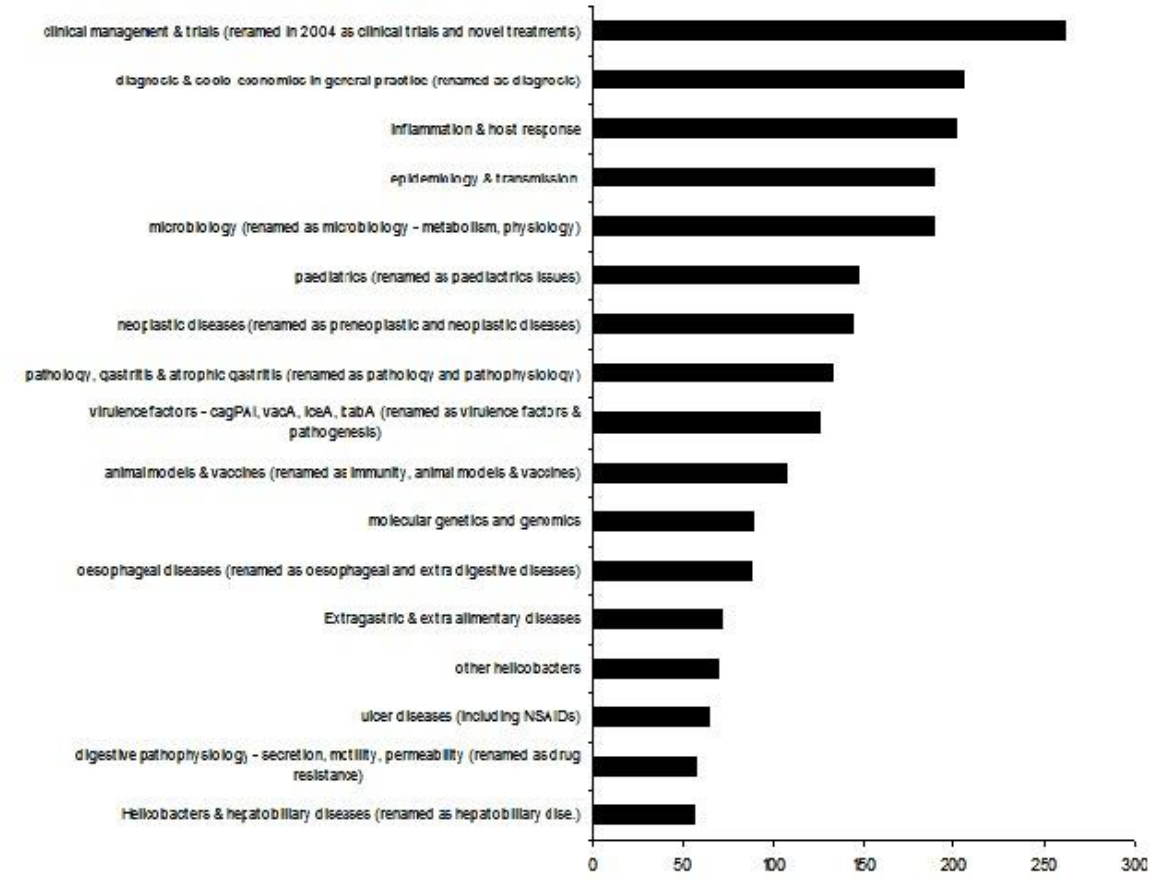
5.7. Overview of the EHSG workshops

Figure 5.21. Papers delivered to annual EHSG Workshops, 1998-2005



Over the period 1998-2005, the number of presentations delivered to ESHG workshops displays a decreasing trend, albeit with two peaks in 2000 and 2003.

Figure 5.21. EHSG workshops thematics by number of papers, 2000-200



Clinical management and trials, Diagnosis and *socio-economics in general practice*, Inflammation and *host response*, Epidemiology and transmission, and *Microbiology*, are the themes framing most of the contributions to the EHSG workshops within this period. The denominations of the themes vary considerably over the period, which may be interpreted as a symptom of the dynamics of the research field. This seems to be corroborated by data concerning the volume of papers per theme and per workshop. Thematic configurations are highly variable from year to year, and some themes end up, in some of the workshops, with no presentations at all. Nonetheless, the "leader" themes for the whole period tend to consistently dominate from year to year, with the exception of Microbiology, which shows a sharp decrease in 2004, after being the main focus in 1998. On the opposite trend, *Oesophageal Diseases* has become the main focus in the 2005 workshop. Other themes with a smaller, but consistent volume of papers are *Pathology, gastritis and atrophic gastritis*, the smaller number of presentations relate to themes such as *Molecular genetics and Animal models and vaccines*.

Finally, some themes display great oscillations over successive workshops, with some of them actually disappearing in some years: *Extra gastric and extra alimentary diseases* (from 2004 on), *Ulcer diseases* (from 2004 on). The fading away of ulcer diseases as a theme may be interpreted as one expression of the saturation and closure of the issue, also mentioned by the researchers who were interviewed. Once again, as noticed in the analysis of words in titles of presentations, the theme *Neoplastic diseases* does not appear as a dominant one, despite the fact that researchers insisted, in interviews and conversations, on its current centrality among their priorities and concerns.

Figure 5.22. Evolution of number of papers by theme, 2000-2005

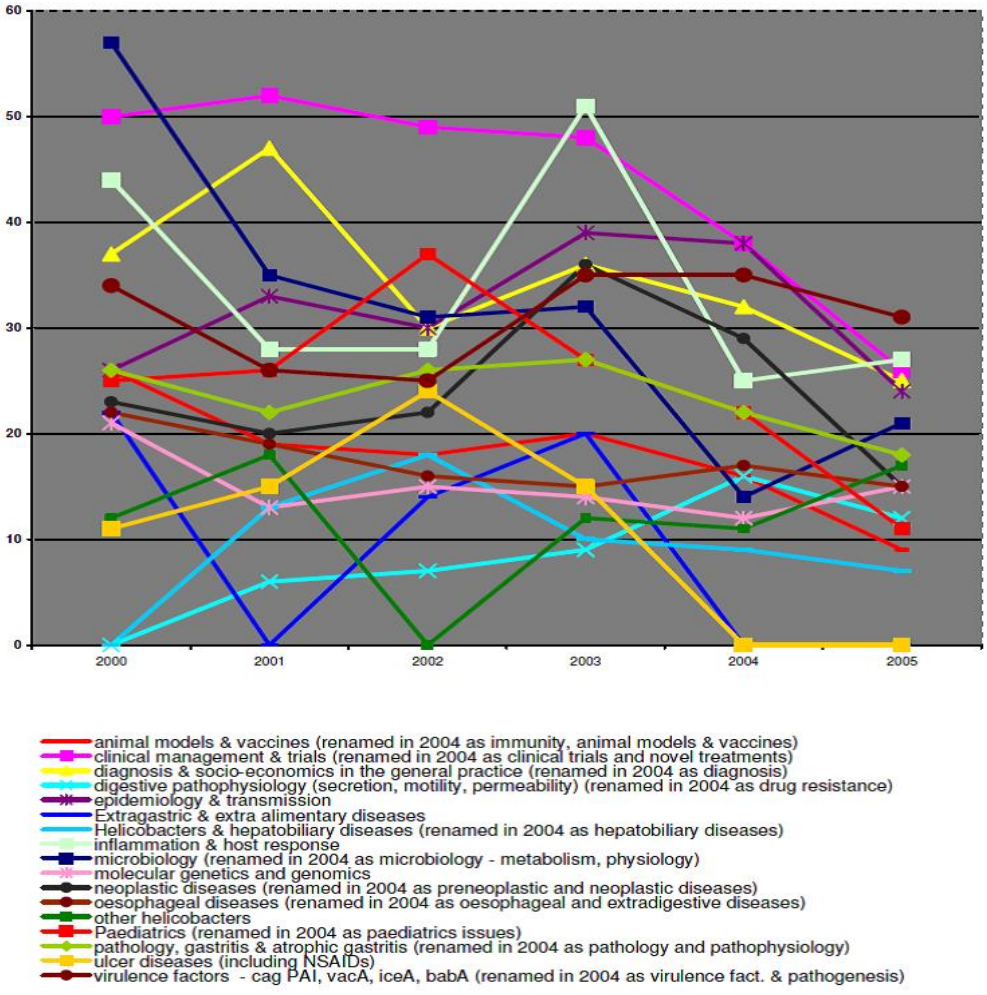


Figure 5.23. Co-word analysis of titles

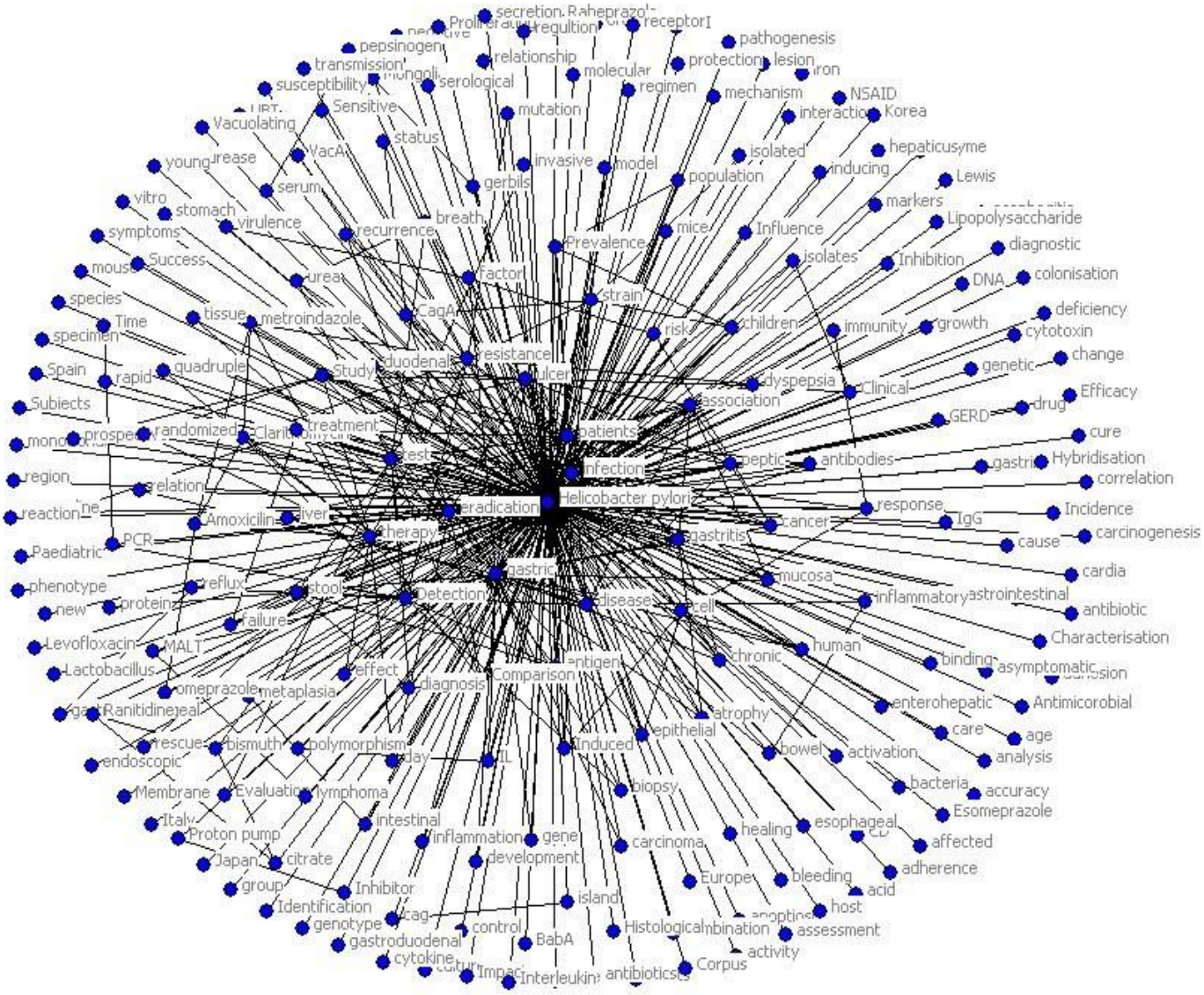
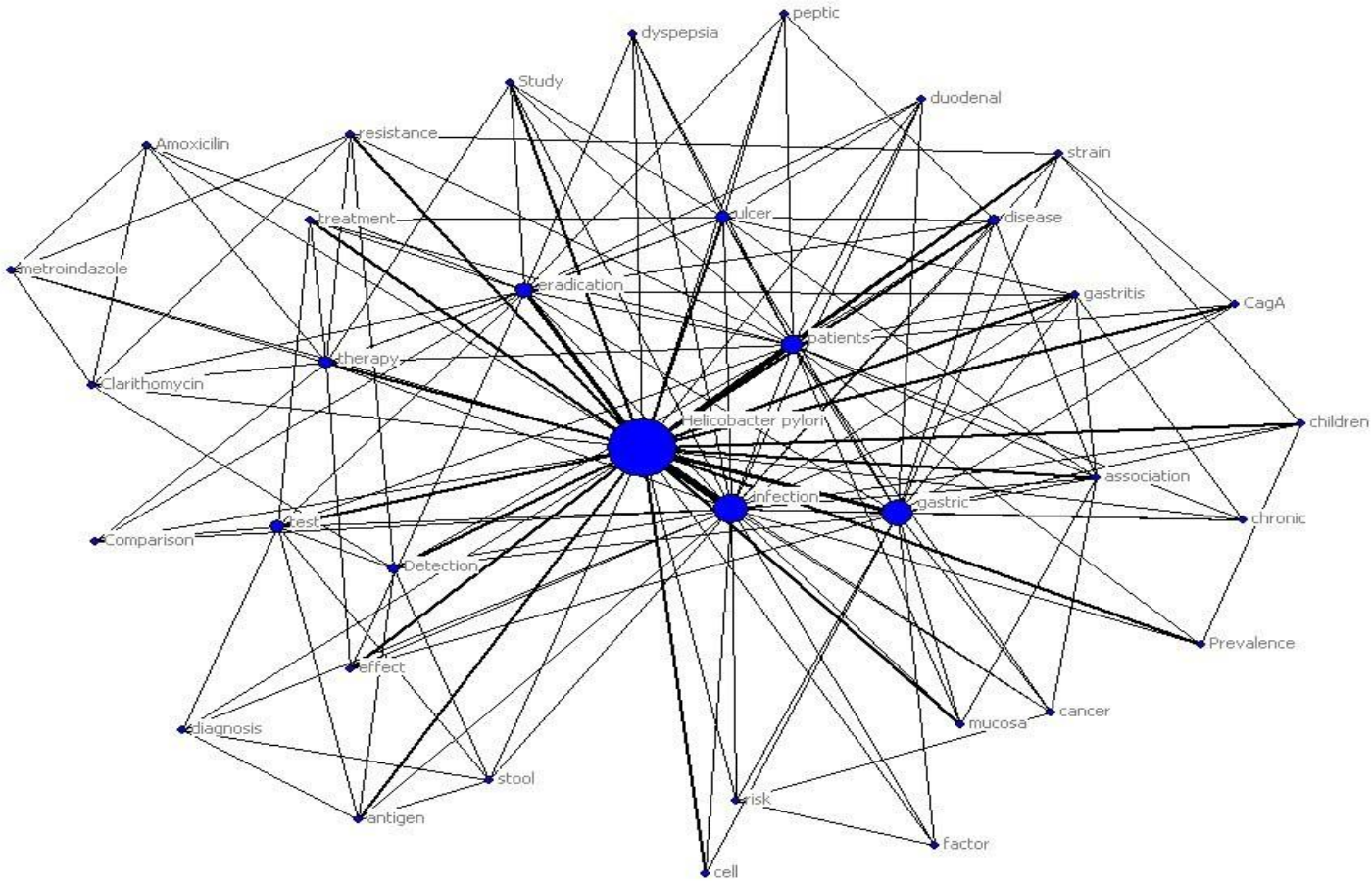


Figure 5.23 is a general map of the co-occurrence of words in the titles of the papers. The next figure contemplates only the words with the highest frequency of ties.

Figure 5.24. Co-word analysis of titles – degree centrality (Nucleus with intensity of ties)



A few words stand out in this figure: *Helicobacter pylori*, *infection*, *gastric*, *patients*, and *eradication*. This would suggest the ongoing definition of the main questions of interest to the group as: the question of infection of the gastric area; the continuous relevance of the debate over eradication; and the relationship to patients, indicating the importance of research directed to clinical settings. Although *disease*, *ulcer*, *therapy*, *test*, and *detection* are words with a smaller number of ties, they are still significant.

The figure underlines the observations of some EHSG researchers in interviews and conversations, who referred to the continuous importance and renewal of studies and debates on the issue of treatment. The increase of antibiotic resistance and the diversity of settings where treatment is prescribed (general/family practice, gastroenterology...) are raising major challenges to the research on treatment, demanding more investigation of different therapeutic regimens, their application and their effects in different contexts and in relation with different manifestations of the diseases, as well as a need for a continuous evaluation of their effects. Again, the data does not display cancer as a theme as prominent as suggested in the interviews. This may be a reflection of the difficulties met by gastric cancer research mentioned by Adrian Lee:

> There's a lot of work to be done on issues of this never ending thing about treatment, but, where it goes is people finally get to gastric cancer. Actually it has become an end point in terms of evidence, and to try to find more evidence to prevention of cancer in the long term is ridiculous, it's obvious it will, but they're impossible experiments (...) there's a lot of later lessons still to be learned there, but the big one is gastric cancer, still number three killer in the world (...).

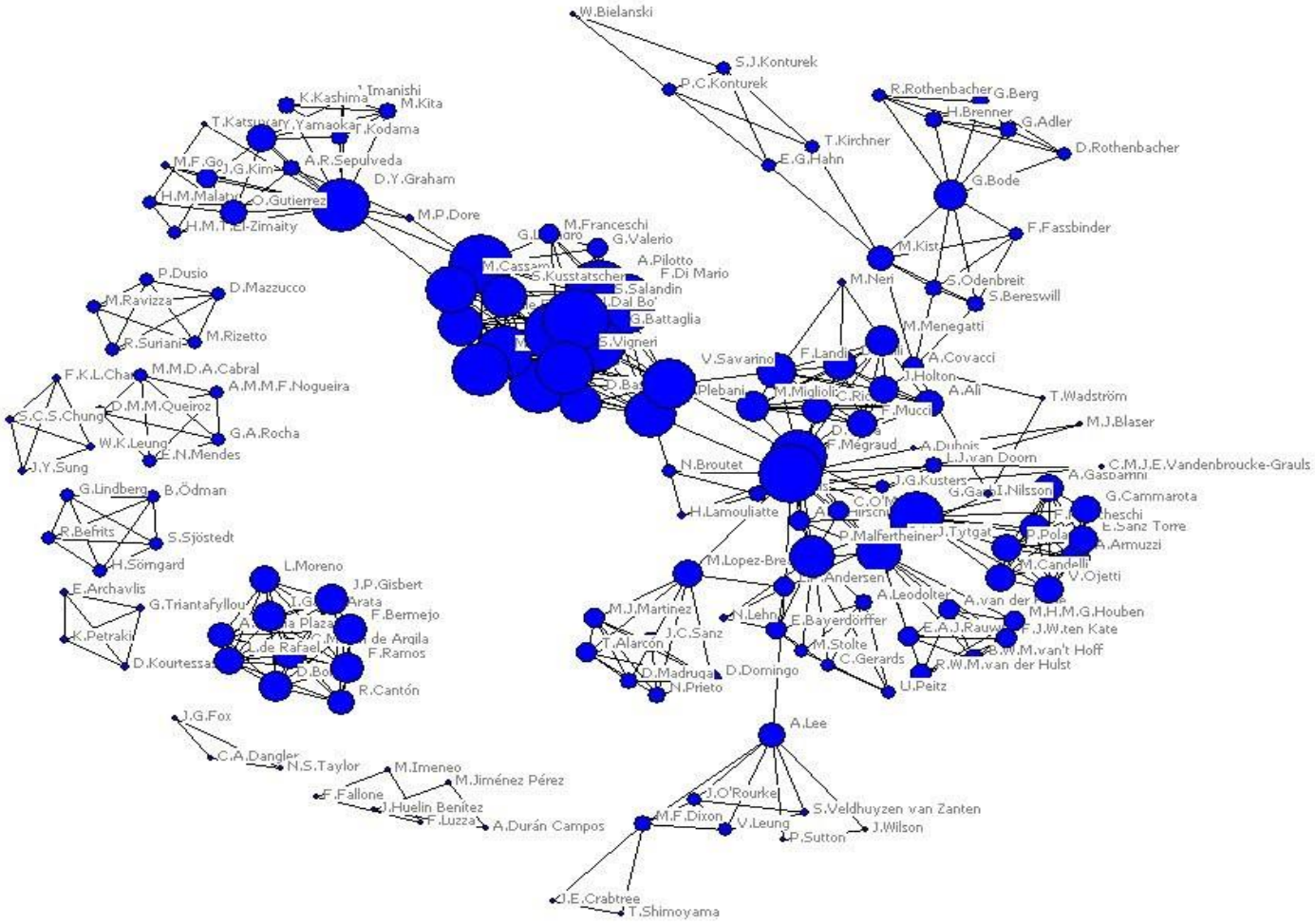
But it also suggests that the themes selected for presentations (which we may assume are those based on research that is actually funded or is more likely to take place in clinical settings) may not necessarily include all those which the community of researchers think are the really big problems to be dealt with in the present and near future, but which do not get adequate funding or are not defined as a priority of health authorities, as is the case of gastric cancer. Another possible factor may be the geographic distribution of researchers. Many of them, and perhaps the majority, come from countries where the very successes achieved in eradicating H.p. have reduced the prevalence and incidence of gastric cancer and thus reduced, at the same time, its visibility as a major health problem.

5.8. Building Collaborative Networks

We move next to the analysis of collaborations between researchers participating in the EHSG Workshops, through co-authorship patterns.[52] First, we present the network of authors, and next we focus on their geographical distribution, according to their country affiliation. The analysis will emphasize the temporal evolution of these patterns, trough three points in time (1998, 2001 and 2004), which provide a rough indicator of major changes in the networks to be traced.

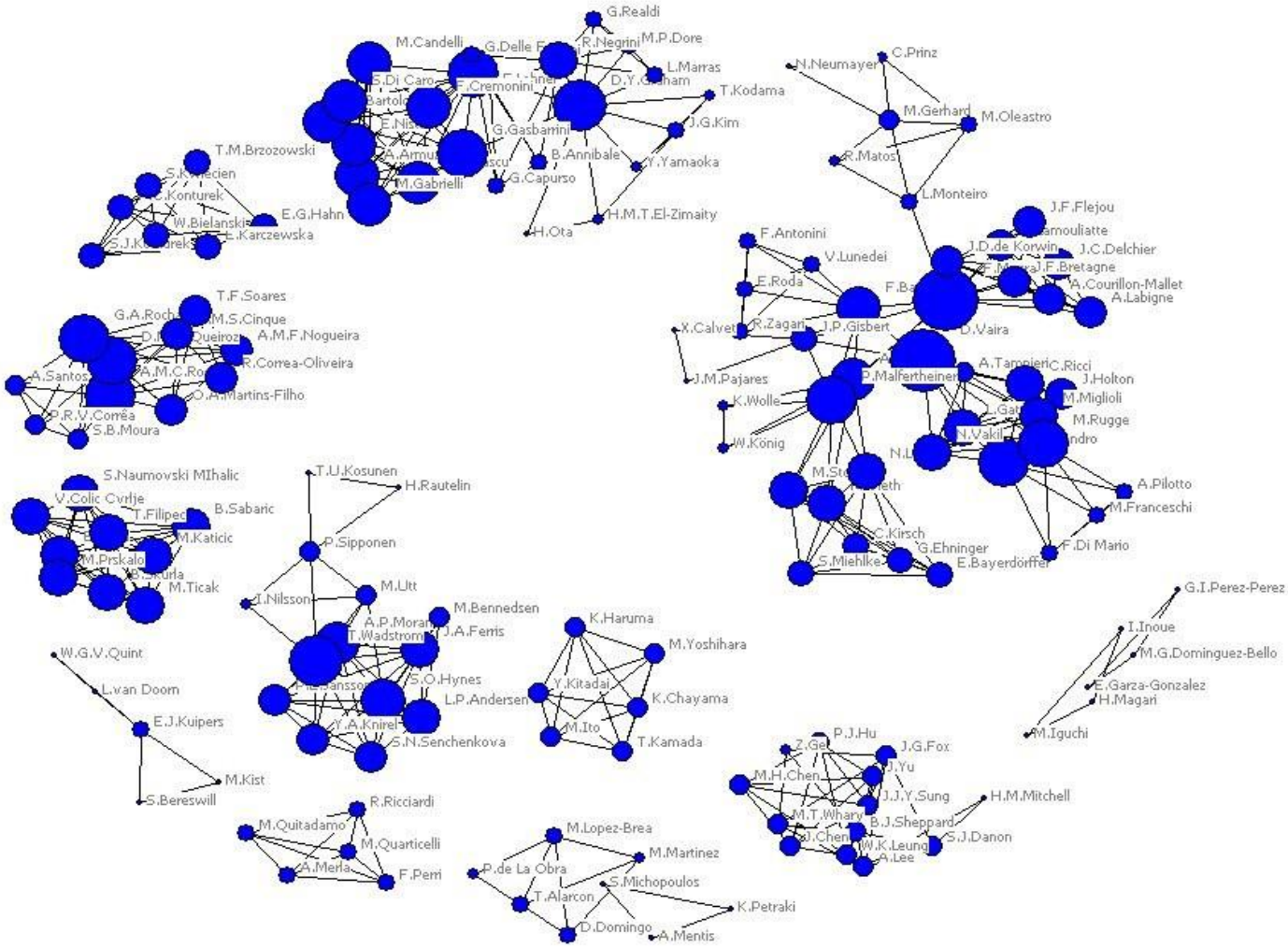
[52] For an exemplary instance of how to analyse collaborative work in the biomedical sciences, see Cambrosio *et al*. (2004).

Figure 5.25. Network of co-authorships (1998) – degree centrality



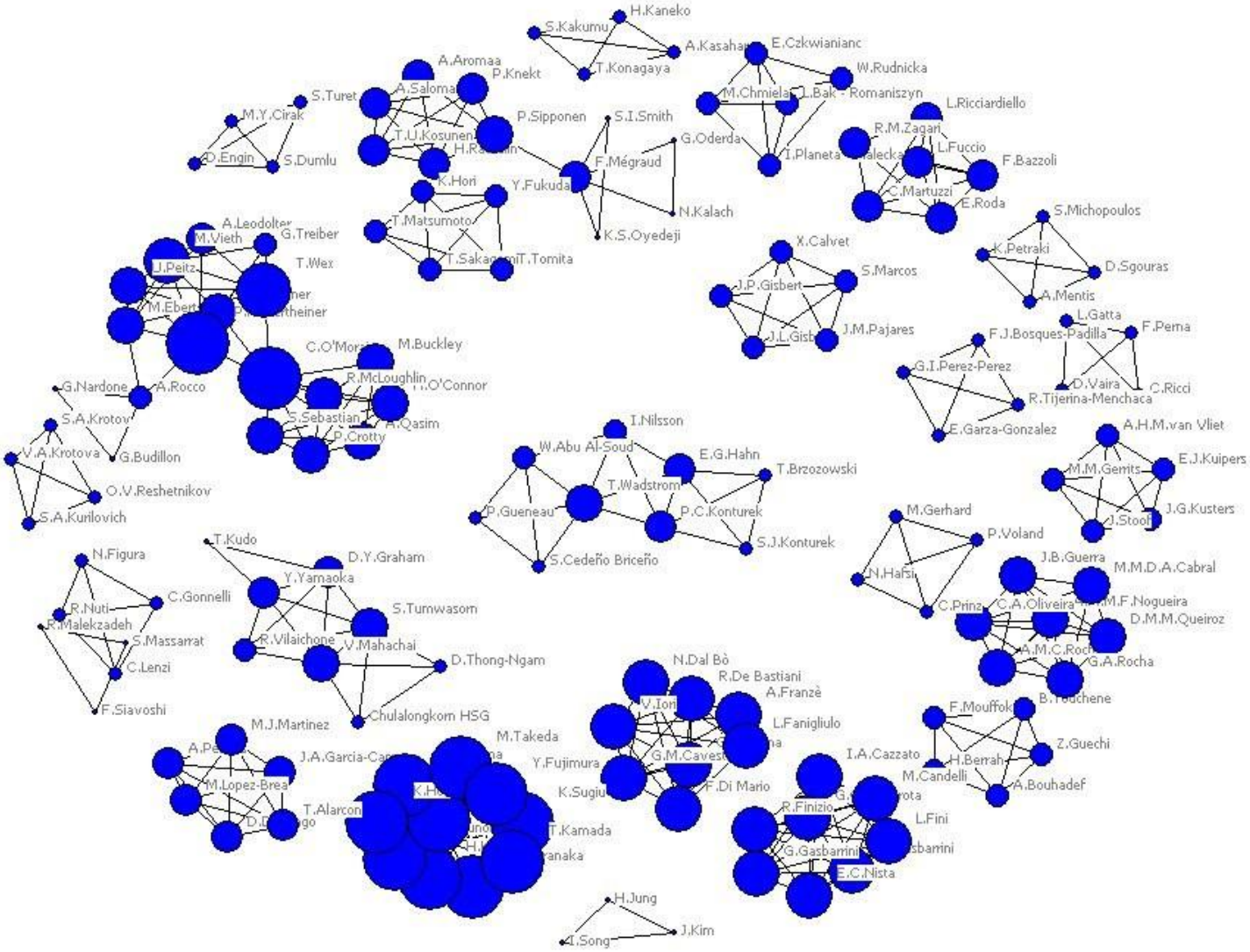
The figure represents the number of ties between co-authors of papers presented in the 1998 workshop. A general overview allows us to identify five major subnetworks, four of them connected to one another. The most noticeable feature of the 1998 workshop is the very frequent collaboration within a central subnetwork of authors based at Italian institutions, tied to several other subnetwoks composed by authors based in a range of different countries, mostly located in the Northern hemisphere.

Figure 5.26. Network of co-authorships (2001) – degree centrality



In comparison with the 1998 map, this figure displays more dispersed and less connected subnetworks. The most relevant subnetwork is multinational, and a second one is mainly composed of authors based in Italy who collaborate mainly with authors located in Japan and the United States. Two other subnetworks should be singled out, one mostly composed by authors based in Brazil (the only significant cluster of collaborations by researchers located in a Southern hemisphere country) and another one based in Sweden.

Figure 5.27. Network of co-authorships (2004) – degree centrality



The 2004 network shows an even more dispersed configuration, with many small, and mostly national subnetworks, with little visible connections to other networks. The significance of this pattern would require further investigation, which it was not possible to carry out due to constraints of time and resources.

It is possible, however, to point to some general trends apparent from a closer scrutiny of the figures. Two main trends are apparent. The first is the expansion of the number of countries involved in collaborations. This, however, is accompanied by a second tendency for collaborations to involve mostly researchers *within* countries and for clusters subnetworks to be less interconnected. And, finally, the contribution of Japan to the overall dispersion and concentration of collaborations, accompanied by a densification of collaborations between researchers and institutions *within* countries.

The frequency and density of collaborations among Japanese researchers and institutions is another noteworthy feature of the situation in 2004. A closer scrutiny of the

data on a year-by-year basis would certainly provide a less coarse picture of the changes in the patterns of collaboration over the whole period, and we expect to be able to offer this analysis in future publications. A final note is in order on the role of the ESHG and its Annual Workshops as a forum for these collaborative initiatives to be widely shared, and as a possible meeting ground of potential collaborators.

Figure 5.28. Countries with more papers contributed to EHSG WSs, 1998-2005 (all authors included)

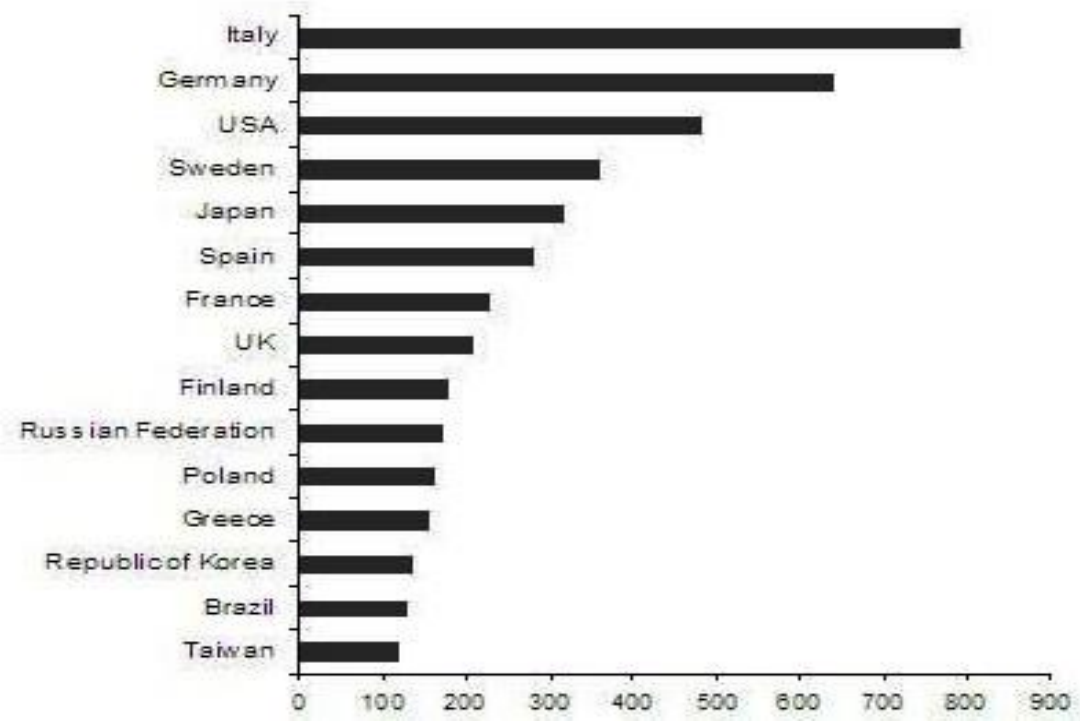


Figure 5.28 above shows the distribution of papers presented at EHSG Annual Workshops from 1998 to 2005 according to the country affiliation of the authors.[53] Again, Italy appears clearly on the lead, followed by Germany. Despite its self-description as "European", the Group has involved countries from other parts of the world from its early years on. The participation of countries like the USA and Japan in contributions to the workshop is highly significant, and this is clearly expressed in the number of contributions, where the USA and Japan rank, respectively, third and fifth.

A detailed analysis of this indicator on a yearly basis reveals that Italy, Germany and the USA share most of the first positions of the ranking, with the exception of 2003 and 2005, when Sweden and Spain were the top contributors.

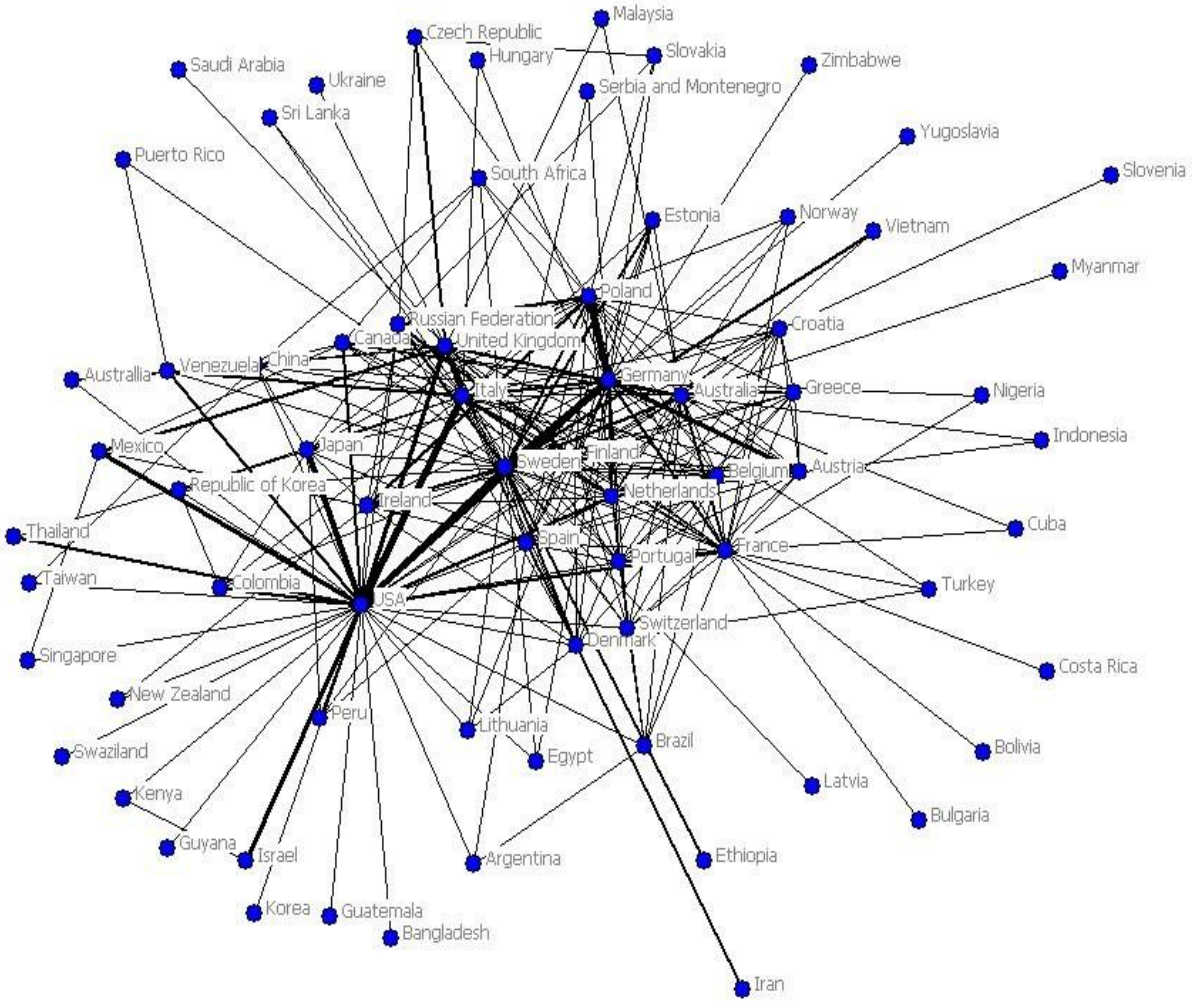
[53] The affiliation of all authors is considered. Since one paper can bee attributed to more than one country (but not more than once to each country), the total figure of country participation exceeds the total number of papers presented.

Table 5.3 Countries participating in EHSG workshops

1998	1999	2000	2001	2002	2003	2004	2005
Australia	Australia	Argentina	Argentina	Argentina	Argentina	Albania	Algeria
Austria	Austria	Austria	Australia	Australia	Australia	Algeria	Australia
Belgium	Belgium	Belgium	Austria	Austria	Austria	Australia	Austria
Bolivia	Brazil	Bolivia	Belgium	Belgium	Bangladesh	Austria	Belarus
Brazil	Bulgary	Brazil	Brazil	Brazil	Belgium	Belarus	Belgium
Canada	Canada	Canada	Bulgaria	Bulgaria	Brazil	Belgium	Brazil
China	China	China	Canada	Canada	Bulgaria	Bosnia Herzegovina	Canada
Colombia	Colombia	Colombia	China	China	Canada	Brazil	Chile
Costa Rica	Croatia	Costa Rica	Colombia	Colombia	Chile	Bulgaria	China
Croatia	Denmark	Croatia	Croatia	Croatia	China	Canada	Croatia
Czech Rep.	Estonia	Croatia	Cuba	Cuba	Croatia	Chile	Cuba
Denmark	Finland	Denmark	Czech Rep.	Czech Rep.	Cuba	Costa Rica	Czech Rep.
Estonia	France	Estonia	Denmark	Denmark	Czech Rep.	Croatia	Denmark
Finland	Germany	Finland	Estonia	Estonia	Denmark	Cuba	Dominican Rep.
France	Greece	France	Finland	Finland	Egypt	Czech Rep.	Estonia
Germany	Guatemala	Germany	France	France	Estonia	Dominican Rep.	Finland
Greece	Hong Kong	Greece	Georgia	Germany	Ethiopia	Egypt	France
Hungary	Hungary	Guyana	Germany	Greece	Finland	Estonia	Germany
Ireland	Ireland	Ireland	Greece	Hong Kong	France	Ethiopia	Greece
Italy	Italy	Israel	Hungary	Hungary	Germany	Finland	Hungary
Japan	Japan	Italy	India	Indonesia	Greece	France	India
Korea	Lithuania	Japan	Iran	Iran	Hungary	Germany	Iran
Lithuania	Mexico	Kenya	Ireland	Ireland	India	Greece	Ireland
Mexico	Netherlands	Lithuania	Israel	Israel	Iran	Hungary	Italy
New Zealand	Norway	Malaysia	Italy	Italy	Ireland	India	Japan
Norway	Poland	Mexico	Japan	Japan	Israel	Indonesia	Kazakhstan
Poland	Rep. Korea	Netherlands	Latvia	Latvia	Italy	Iran	Lithuania
Portugal	Russian Fed.	New Zealand	Lithuania	Lithuania	Japan	Ireland	Malaysia
Rússia Fed	Singapore	Norway	Mexico	Mexico	Lithuania	Israel	Mexico
Singapore	Slovenia	Poland	Myanmar	Netherlands	Mexico	Italy	Netherlands
South Africa	South Africa	Portugal	Netherlands	New Zealand	Netherlands	Japan	Nigeria
Spain	Spain	Rep. Korea	Norway	Nigeria	Nigeria	Latvia	Pakistan
Sweden	Sweden	Romania	Poland	Norway	Norway	Lithuania	Poland
Switzerland	Switzerland	Singapore	Portugal	Peru	Pakistan	Macedonia	Portugal
Taiwan	Taiwan	Slovenia	Rep. Korea	Poland	Peru	Malaysia	Rep. Korea
Netherlands	Turquey	South Africa	Russian Fed.	Portugal	Poland	Mexico	Russian Fed.
Turkey	UK	Spain	Saudi Arabia	Rep. Korea	Portugal	Netherlands	Serbia Montenegro
Ukraine	USA	Sweden	Slovakia	Romania	Puerto Rico	New Zealand	Slovenia
UK		Switzerland	South Africa	Russian Fed.	Rep. Korea	Nigeria	Spain
USA		Taiwan	Spain	Singapore	Russian Fed.	Norway	Sri Lanka
Yugoslavia		Turkey	Sweden	Spain	Saudi Arabia	Poland	Sweden
		UK	Switzerland	Srilanka	Singapore	Portugal	Switzerland
		USA	Taiwan	Sweden	South Africa	Rep. Korea	Taiwan
		Uzbekistan	Thailand	Switerland	Spain	Russian Fed.	Thailand
		Yugoslavia	UK	Taiwan	Sweden	Singapore	Turkey
			USA	Thailand	Switzerland	Slovakia	UK
			Venezuela	Turkey	Taiwan	South Africa	USA
			Yugoslavia	Ukraine	Thailand	Spain	Uzbekistan
				UK	Turkey	Sri Lanka	Venezuela
				USA	Ukraine	Swaziland	
				Venezuela	UK	Sweden	
				Vietnam	USA	Switzerland	
				Yugoslavia	Venezuela	Taiwan	
					VietNam	Thailand	
					Yugoslavia	Turkey	
						UK	
						Ukraine	
						USA	
						Uzbekistan	
						Venezuela	
						Zimbabwe	

The previous table allows us to verify the great diversity of the countries where researchers participating in EHSG Workshops are based. Indeed, the "European Group" is not confined to Europe. It involves researchers from all regions of the world, even though their distribution in terms of numbers does not overlap with the global map of infection by H.p.. Attendance will depend on access to funding, which is highly variable across countries and regions, and varies in intensity over the period under analysis. The EHSG workshops, nonetheless, provide a unique forum for researchers across the world to meet and thus have become the major event in the field of research on H.p.. Collaborations between different institutions of the same country and between institutions based in different countries allow a more precise picture to emerge.

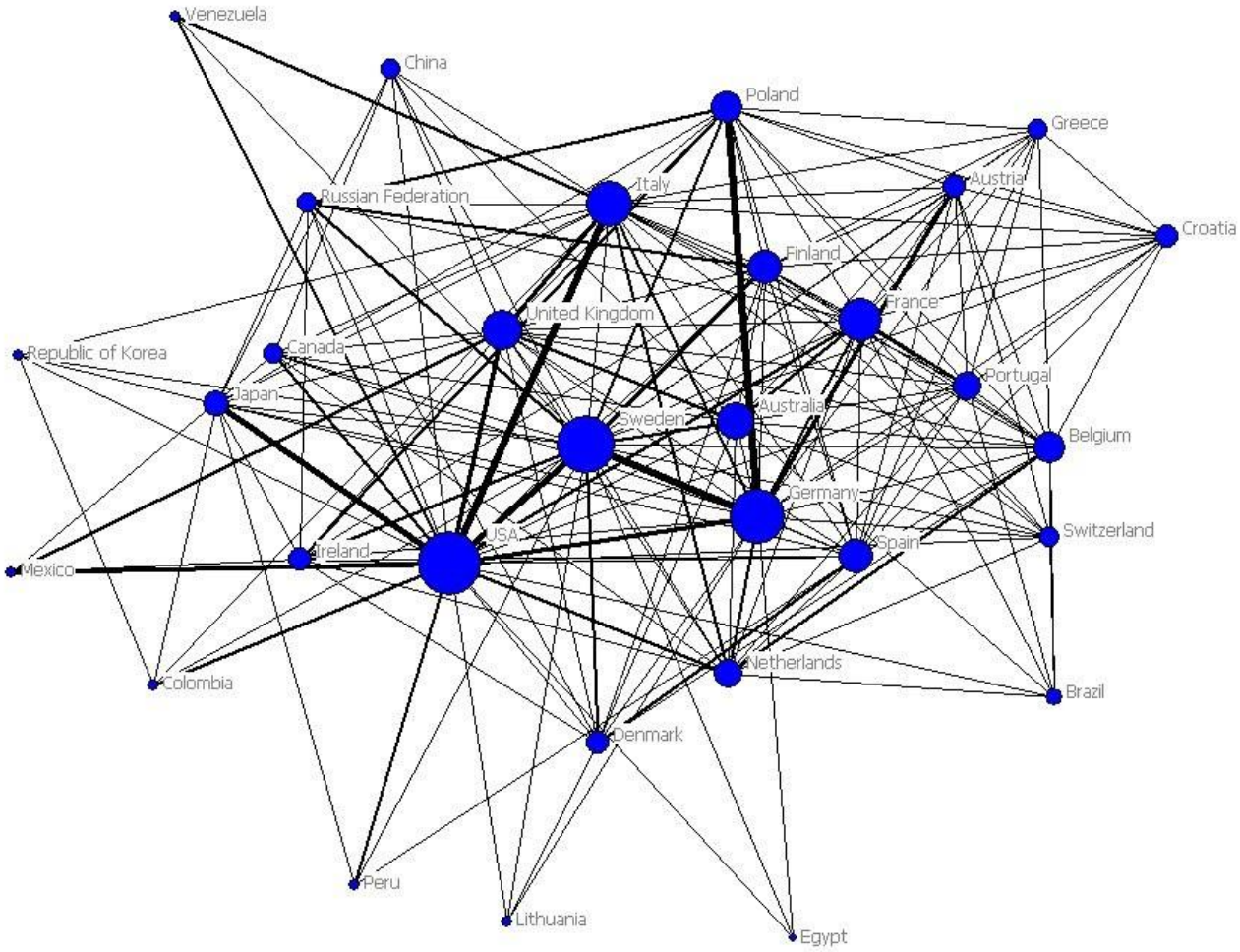
Figure 5.29 -Participating countries and intensity of ties within and between countries[54]



[54] Intensity of ties is proportional to the thickness of lines.

It is interesting to note that, as might have been expected, the network is dominated by European countries, who occupy the central positions, reflecting their strong interlinked network. The countries previously identified as having the highest number of participations – Italy, Germany and USA – also have a particularly high number of links, together with Sweden, but the USA (as well as Japan) is positioned slightly outside the European core, and is at the centre of the specific network.

Figure 5.30. Countries with highest degree centrality – core (intensity of ties)[55]



The countries displaying more frequent and intense internal collaborations are the USA, Sweden, Germany, France, Italy, and UK. This is likely to be a function of the number of institutions and research groups involved in research on H.p. within each country. These

[55] Intensity of ties is considered both for collaborations within countries, i.e., involving several institutions in the same country (expressed by the size of the circles), and for collaborations between countries (expressed by the thickness of the lines).

leading countries are followed by Finland, Poland, Australia, Belgium, Spain, Portugal, Netherlands and Japan. Collaboration between specific countries is more intense between Sweden and Germany, Germany and Poland, the USA and the UK, Sweden and the USA, Japan and the USA, and with less but still significant frequency between the Russian Federation and Poland, Finland and Sweden, Germany and Austria, and the USA and Germany and the USA and Mexico. A double pattern of frequent and intense international collaborations seems to emerge from this analysis. Neighbouring countries seem to be more likely to enter these collaborations, as is the case with Sweden and Germany, Germany and Poland, Finland and Sweden or, at least in part, the USA and Mexico. The second pattern is based on the centrality of the USA. In this case, the resources available in the USA and the activity of research groups and institutions located in that country become powerful attractors for potential collaborators in other countries.

5.9. Discussion

We did not try to compare the data on the EHSG with data obtained in the SCI database since the sources, the contexts, and the time span covered do not coincide.

A longer time series of data on the EHSG and a year-by-year analysis of available data would have allowed us to improve and deepen the analysis and interpretation offered in the preceding sections. Despite these limitations, this exercise offered a number of preliminary insights into a theme which deserves further investigation. Some major trends characterizing the dynamics of the field of research on H.p. have been highlighted, and a first description of the structure and evolution of what is currently the main forum of the field and the main collaborative initiatives within the field provides a picture of the networks of researchers, countries and themes which configure the latter. This picture requires continuous updating. The 2005 EHSG Annual Workshop witnessed a decrease in participation, and a closer look at how participation evolved – and at its distribution by country and theme – in the following years is needed to get a more accurate picture of where the field is going, and in particular how some of the emerging concerns with issues such as the links to gastric cancer or the current problems with eradication strategies will actually shape the future of field. We expect to pursue this work and provide materials to ESHG members and Workshop participants for a reflection on the past and future of the Group and, more generally, of research on *Helicobacter pylori*.

6. Ontological variability: performing the variable virulence/pathogenicity of *Helicobacter pylori*

6.1. Introduction

This chapter has three objectives. The first is to present 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 existence 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 third and final objective is to provide an instantiation of what we will call the ontological variability of *Helicobacter pylori* and how this ontological variability is itself produced as the outcome of research and clinical practices.

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 (2002: 17-18),

> 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.

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" (Fleck, 1979/1935: 61) 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 social studies of biomedicine and health and in studies in the history of medicine and health, especially those informed by science studies.[56] Recent contributions to science studies and "naturalistic" philosophy of science (Rouse, 2002, 2004; Callebaut, 1993), have

[56] See, for instance, Latour (1984); Mendelsohn (2001); Geison (1995, 2002); Geison and Laublicher (2001); Eckart (2002); Bynum (2002); Worboys (2000); Cukierman (2007); Löwy (2001); Creager (2002).

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 productive of new objects in a diversity of settings, ranging from the laboratory and the clinic to everyday situations.

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 (Barad, 2007).[57] Following the modes of existence of biomedical phenomena and the processes through which they are brought to existence and to make a difference provides a productive approach to the "ontology in movement" called for by Daston (2000). The latter is inextricable from knowledge-producing practices and from their accountability as part of a world in ongoing processes of reconfiguration. This chapter attempts to explore where these insights may take us through the elucidation of the modes of existence of the 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. We thus engage with 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 (Rheinberger, 1997) – an object which, even when stabilized and mobilized in further experimental or observational practices, is (re)enacted to search for new differences (Rouse, 2002) -, as an established biomedical fact, and as a genetically diverse 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 (2002, 2004) and Karen Barad (2007), and by re-readings of recent contributions to the social studies of biology and biomedicine, including those by Mol (2002), Keating and Cambrosio (2003), Rheinberger (1997) and Rabinow (2003), among others.

The first section of the chapter offers a more detailed presentation of the approach, and is followed by a summary of the history of the emergence and diverse enactments of

---

[57] See Mol (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" (Barad, 2007). For detailed accounts and discussions of the production of biological and biomedical objects and entities as material/discursive or material/semiotic practices, see Rheinberger (1997) and Keating and Cambrosio (2003). Rabinow's recent work (2003, 2008) offers powerful insights into the performance of differences in the world and how they may be observed and accounted for. We return to the convergences as well as to the differences between some of these approaches in the final chapter of this report.

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.

6.2. The approach

As mentioned above, the approach we introduce next draws on the recent work of Karen Barad (2007) and Joseph Rouse (2002, 2004).[58]

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" (Rouse, 2004: 146). "Reproducible" should not be understood as being related to actual repetition or regularity, but rather to *repeatability*: "what matters is not the exact reproduction of the same sequence of events, but the reproduction of a significant 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" (Rouse, 2004: 147).

Barad draws on what she describes as Niels Bohr's *philosophy-physics* toprovide working definitions of what phenomena are. According to Bohr, the term should be applied "exclusively to refer to the observations obtained under specified circumstances, including an account of the whole experimental arrangement" (quoted in Barad, 2007: 119). 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 (Barad, 2007: 206, italics in original).[59]

Phenomena are thus "material configurations of the world, which are frequently, but not exclusively the product of scientific research" (Rouse, 2004: 147).

But phenomena also appear as "material configurations of the world", in that they "constitute a practical or `constructed´ cut between a measuring apparatus and a measured

---

[58] Our use of the work of these and other authors takes the form of what Barad (2007) calls a "diffractive" reading of a range of contributions to science studies 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.

[59] 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, 2007: 128). For a more detailed treatment of this point, see Barad, 2007, especially Chapters 3 and 4.

`object´.[60] No inherent boundary divides an object from its surroundings, for the location of the cut depends upon the configuration of the apparatus" (Rouse, 2004: 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). (Barad, 2007: 203)[61]

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.[62] Apparatuses should thus not 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 (Barad, 2007: 171-172 and note 434, note 65).

Within this framework, virulence/pathogenicity may be defined as the outcome of a set of material-discursive practices constitutive of specific 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

---

[60] 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.

[61] For a different, but not unrelated approach to apparatuses and to observation, see Rabinow (2003), especially pp. 49-55, and (2008).

[62] See Barad (2007) for a fuller discussion of these points. Readers familiar with the work of Rheinberger (1997) and Keating and Cambrosio (2003) will notice that the former's experimental systems or the latter's biomedical platforms may be redescribed as measuring apparatuses as defined by Barad. The same holds for the relationship between pragmatism's "effects" (see Chapter 2) and Barad's phenomena. A fuller discussion of these topics is beyond the scope of this project and would require separate treatment.

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, which will be commented in more detail in the concluding section. More generally, it points towards the 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.[63]

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 science studies 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 (Latour, 1999: 119-120; Nunes, 2004) and displaying its performative quality (Rouse, 2004: 151; Barad, 2007).[64]

In the terms of the framework adopted here, this movement would correspond to the intra-active process whereby "actions" produce the material/semiotic boundaries differentiating "objects" and "agencies of observation".

The papers we have drawn upon were published between 1998 and 2000 and brought together as the doctoral dissertation of their main author, submitted in 2000 (Figueiredo, 2000; Figueiredo *et al.*, 2000; van Doorn *et al.*, 1998a, 1998b, 1998c, 1999a, 1999b).[65] 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.

A detailed account of all the practices through which the variable virulence/pathogenicity of H.p. is enacted as a phenomenon, or of the range of apparatuses involved, would far exceed the scope of this project. We 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 chapter, is equated with the work reported in the papers I have analysed, may itself be approached as a phenomenon.

Let us start by briefly revisiting the story of the making of *Helicobacter pylori* as a biomedical entity and as a pathogen, but with a specific focus on the variable ontologies of H.p.

---

[63] For discussions of these points, see Barad (2007), especially Chapter 8 (pp. 353-396) and Rouse (2004: 154-156).
[64] On the convergences and differences between this approach and actor-network theory, see the concluding section.
[65] All quotations are from the versions included in Figueiredo (2000).

6.3. *Helicobacter pylori* and its variable ontologies

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 of the gastric region by bacteria was generally seen as an impossibility, due to the inhospitable environment which, through secreted acids, allegedly kept the stomach sterile.[66] Warren and Marshall, however, found a strong association between several forms of common gastric disease, such as chronic gastritis and peptic ulcer disease, 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 a range of different and parallel research lines, involving several specialties in biomedicine, including gastroenterology, and microbiology. Identified at first as a species of an already known genus, *Campylobacter*, and christened accordingly *pyloric campylobacter*, *Campylobacter pyloridis* and later *Campylobacter pylori*, the new bacterium would finally be recognized as part of an altogether different genus and renamed *Helicobacter pylori* (H.p.) in 1989 (Goodwin, 1994).[67]

Over the decade following its successful culture, H.p. would become the subject of an increasing number of publications (next figure) 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

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

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

[66] See the contributions included in Marshall (2002).

[67] For a useful overview of the setting and chronology of early work on Helicobacter pylori, see Thagard (1998a and b, 1999). Beyond more general disagreements on Thagard's epistemological and theoretical commitments and on his treatment of science studies, this project 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 follow the ways in which a specific biomedical entity is performed through narrative reconstructions and practices practices.

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 (Dixon *et al*., 1996: 1161).

These guidelines, known as the Updated Sidney System, were published in *The American Journal of Surgical Pathology* in 1996, and have become an obligatory passage point (Latour, 1987) for clinicians and clinical researchers. In 1997, the first Maastricht Consensus Report established further guidelines for the management of H.p. infection. By 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. (Tomb *et al.*, 1997). 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 epidemiological 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 a passage which is worth quoting at length:

> *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 lymphoid 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 (Figueiredo, 2000: 205).

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, 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). 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 (Figueiredo, 2000: 206).

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 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.

6.4. 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" (Figueiredo, 2000: 171). 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 epidemiological 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.

By the late 1990s, 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; assays used for serological analysis (Helicoblot versions 2.0 and 2.1, Pyloriset screen CagA, DDL prototype CagA assay, Vanderbilt University anti-CagA EIA); 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 specific 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" (Figueiredo, 2000, 23).

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 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 (Figueiredo, 2000: 23-25).

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). In fact, 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.

Finally, the distribution of strains defined by specific genotypes is characterized through epidemiological studies. Recall that the expression "virulence-associated genes" is "largely based on clinical and epidemiological observations" (Figueiredo, 2000: 23). "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.[68]

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.

---

[68] "[I]ntelligibility is a matter of determinateness (an ontological notion [as opposed to the epistemological notion of certainty] through which what matters – materially and semantically – is "spelled out"). It is not a human-based epistemological conception" (Barad, 2007: 444, note 34).

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-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. (Figueiredo, 2000: 28). 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).[69]

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".[70] The fragments thus obtained, after amplification, 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". 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, in this case 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 (Figueiredo, 2000: 28).

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

---

[69] This particular apparatus thus displays features of what Keating and Cambrosio (2003) define as a biomedical platform. See the last section for further discussion.

[70] 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" (Kevles and Hood, 1992: 382). On the invention and development of PCR, see Rabinow (1996).

from patients; a nitrocellulose strip carrying oligonucleotide probes; a human agent operating PCR and performing the assay; laboratory equipment for the performance of 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 structure" of the genes, making available for analysis variable alleles, the cut performing now these genes as objects.[71]

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 their terms, 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.

6.5. Discussion

The framework presented and discussed in this chapter may be read 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 ontology that is true to objects that are at once true and historical" (Daston, 2000: 14). 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

[71] For detailed information on the sequence of operations and materials involved and a description of the results, see Figueiredo (2000: 47-50, 62-63, 69, 79-80, 148-149).

philosopher Joseph Rouse. Following Barad's lead, we have engaged in a "diffractive" way with their work. This "diffractive" reading included a wide range of contributions to the science studies 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 this section, we would like to engage more explicitly with some of these contributions.

Let us 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 chapter. 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 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).

Readers may identify as well some family resemblances with Annemarie Mol's (2002) performative approach to medical practices and to "ontological politics", with Hans-Jörg Rheinberger's (1997) account of experimental systems and the performance of epistemic objects, or with Keating and Cambrosio's (2003) concept of "biomedical platforms", to mention only some of those contributions which were particularly relevant for the topic of this paper.

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 notion of "ontological politics", as a shorthand for the performativity of medical practices, is a significant resource for the ethico-onto-epistemo-logical reconfiguration called for by Barad (2007).

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" (2003: 332). 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" (Keating and Cambrosio, 2003: 332), or, in other words, that it is the platform that defines these entities and actors through the specific differentiations and boundaries it enacts. The second approach

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 (1997) 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 science studies or sciences studies-informed research on the diversity of both scientific practices and of the phenomena and objects they enact. This chapter may thus be read as an exploration of how time-honoured topics of both biological and biomedical research and of science studies may be approached through these reconfigurations.

7. Concluding Remarks

In July 2005, when this project was starting, Robin Warren and Barry Marshall were awarded the Nobel Prize for Medicine or Physiology for their work on Helicobacter pylori and its relation with common gastric diseases. For some, this was an overdue recognition of a highly significant achievement. For others, it signalled the triumph of a time-honoured style of medical research with its roots in the pioneering work of the early bacteriologists. For others still, its significance lay in the fact that, this time, the Nobel Prize rewarded work which had had a visible and significant impact on the lives and well-being of millions of patients in the world. It did not go unnoticed that there was little talk of genes, genomes or cutting edge topics or technologies. An infectious agent had been identified, isolated and cultured and its causal links to common gastric diseases demonstrated, opening the way to effective diagnosis and therapy of these diseases. Warren and Marshall had shown that there were modest roads leading to the Nobel, without the need to yield to hype and seeking to appear on the headlines. In any case, this was the crowning achievement of a long process, beginning in the late 1970s. Helicobacter pylori was now an obligatory passage point for gastroenterologists and patients suffering from gastric diseases and Warren and Marshall were the main spokespersons for the bacterium and for the attachments and associations endowing it with reality.

The preceding chapters have traced some of the key episodes in the path leading from the early observations of bacteria growing in the human stomach, through the declaration of their non-existence, to the successive moments in which the contentious reality of the bacterium was established, its association with gastritis and peptic ulcer disease was proposed and its causal role in these conditions was demonstrated. Throughout a succession of trials, the ontology of the bacterium was successfully redefined, through the addition of new effects associated with it and displayed through an array of laboratory and clinical practices and the production of a variety of inscriptions culminating in a series of publications issued between 1983 and 1985. The moving ontology of the bacterium was mirrored in the successive names it was given, from the general description of "spiral bacterium" or "spiral shaped bacterium", through "Campylobacter-like Organism", "pyloric Campylobacter", *Campilobacter pyloridis*, *Campylobacter pylori* and, finally, *Helicobacter pylori*, each of these names associated, in turn, with a range of effects made visible through the trials the bacterium was subject to and its associations with other entities. Salience, emergence, productivity and embeddedness (Daston, 2000) were inextricably linked throughout this story.

The final stabilization of the name of the bacterium, in 1989, would coincide with the beginning of a decade characterized by the expansion of the actor-network that emerged over the previous years. The 1990s would, indeed, witness the elaboration of a number of consensus statements and guidelines for the diagnosis and management of infection by *Helicobacter pylori*, thus strengthening the associations endowing it with reality: NIH Consensus Statement (1994), Maastricht Consensus Statement (1996), Updated Sydney System (1996), specifying guidelines for the description and classification of gastritis. By the end of the decade, the gastroenterology community had officially changed its allegiance to previous views to embrace *Helicobacter pylori* as an obligatory passage point for the diagnosis, management and therapy of common gastric diseases. New therapies for these diseases, through eradication of the bacterium, became standard tools of gastroenterology. Research and publications on the subject went through considerable growth after the mid-

1980s and until the late 1990s. In 1994, H.p. was declared by the International Agency for Research on Cancer a type I carcinogen (the first bacterium ever to have that status, and another move in its ontological status). In 1997, the first sequencing of the genome of a strain of H.p. was published in *Nature*. Some countries established selective screening for H.p. infection and programs for its eradication, achieving significant results in the reduction of gastric disease in general and severe conditions like gastric cancer in particular. An international research group on *Helicobacter* (European Helicobacter Study Group), holding annual workshops since 1988, and a specialized journal, *Helicobacter*, reinforced the organizational basis for research on the bacterium. Genetic research on H.p. allowed the genotypes of different strains to be mapped and their clinical and epidemiological relevance to be assessed, as well as their importance for studies in population genetics. The association of H.p. with gastric cancer and with other types of diseases became central research themes and clinical concerns.

This report offers some partial accounts of this story. Much has been left out, for reasons ranging from constraints of time and resources to the recognition that many of the topics mentioned above would require specific projects. And, of course, the story is far from having come to an end. The ontology of *Helicobacter pylori* has not ceased to move, and contention and controversy are still present. If the reality of the bacterium and of its pathogenic effects is no longer in doubt, new discussions have emerged associated with the possible protective effect of H.p. for some diseases of the upper gastric tract, or the decreasing effectiveness of eradication therapies in some countries. But some exciting recent developments threaten to move H.p. to the forefront of biomedical and biotechnological innovation: Barry Marshall has embarked on the attempt at using strains of H.p., genetically modified to reduce their virulence, as carriers of vaccines.

Throughout this project, further and interesting directions of research popped up, which would provide the ground for future projects. Some of these may be suggested here:

- The first would be a detailed account of the various meetings and working groups which produced consensus statements, guidelines and the 1994 IARC declaration. These will require a research effort broad in its geographic scope, which would include the identification of and contact with members of these groups and committees, access to documents (where possible) and the collection and processing of first- person accounts. Some scattered information on these events was collected for this project, but proved insufficient for a full-fledged treatment of the topic.

- A second possible follow-up to this project would be the treatment of the considerable volume of data collected on international research collaborations and networks, which could only be partially used for this project (see Chapter 5), mainly due to the amount of time and resources needed for processing and exploring all the information. We expect to pursue some of this work after the closure of this project, namely through a broader study of the European Helicobacter Study Group.

- A third project would be an investigation of the forms of biological or biomedical citizenship (Petryna, 2002) associated with the programs for screening and eradication of H.p. These would involve the definition of which particular groups of citizens are selected and on what criteria for the different national programs or initiatives, a description of the

latter and an analysis of their implementation and public assessment. Such a study would add to the growing literature on access to citizenship rights - namely of the right to medical care - through treatment of specific health problems.

• A fourth possible follow-up involves the development of a theme touched upon by Barry Marshall in the final part of his chapter in Helicobacter Pioneers (Marshall, 2002: 1999-200) and which would deserve a full-fledged investigation: the role of the pharmaceutical industries and public funding agencies in relation with the various stages of the history of H.p.

• Finally, the work currently led by Barry Marshall on the use of genetically modified H.p. strains as carriers of vaccines would merit close attention and a study in the line of what Rabinow and his collaborators (see Rabinow and Dan-Cohen, 2005) are doing for genomics, due to its potential to become a major breakthrough in biomedicine and biotechnology, which can be followed and chronicled in real time.

Not all of these follow-ups will be viable in the short term. We expect that at least some of them (such as the second and possibly the third) may be pursued in the near future. For the time being, our main task is to further explore the materials and results produced as part of this project and share them through publications, including a book to be submitted to an international publisher within the next two years.

References

Barad, K. (2007), *Meeting the Universe Halfway: Quantum Physics and the Entanglement of Matter and Meaning*. Durham, North Carolina: Duke University Press.

Bazerman, C. (1988), *Shaping Written Knowledge: Essays in the Growth, Form, Function, and Implications of the Scientific Article*. Madison: University of WisconsinPress.

Burnett, R.A. *et al.* (1984) "Campylobacter-Like Organisms in the Stomach of Patients and healthy Individuals", *The Lancet*, 16 June, 1349.

Bynum, W. F. (2002), "The Evolution of Germs and the Evolution of Disease: Some British Debates, 1870-1900", *History and Philosophy of the Life Sciences*, 24 (1): 53-68.

Callebaut, W. (1993), *Taking the Naturalistic Turn: How Real Philosophy of Science is Done. Chicago*: University of Chicago Press.

Callon, M. (1999) [1986], "Some Elements of a Sociology of Translation: Domestication of the Scallops and the Fisherman of St. Brieuc Bay", *in* Mario Biagioli (Ed.), *The Science Studies Reader*. New York and London: Routledge, 66-83.

Cambrosio, A. *et al*. (2004), "Mapping Collaborative Work and Innovation in Biomedicine: A Computer-Assisted Analysis of Antibody Reagent Workshops", *Social Studies of Science*, 34 (3), 325-364.

Cicolella, A.; Browaeys, D. B. (2005), *Alertes santé: experts et citoyens face aux intérêts privés*. Paris: Fayard.

Clarke, A.C. (2005), *Situational Analysis: Grounded Theory After the Postmodern Turn*. Thousand Oaks: Sage.

Clough, S. (2003), *Beyond Epistemology: A Pragmatist Approach to Feminist Science Studie*s. Lanham: Rowman and Littlefield.

Collins, H. (1975), "The Seven Sexes: A Study in the Sociology of a Phenomenon, or the Replication of Experiments in Physics", *Sociology*, 9, 205-224.

Creager, A. (2002), *The Life of a Virus: TMV as an Experimental Model, 1930-1965*. Chicago: University of Chicago Press.

Cukierman, H. (2007), *Yes, nós temos Pasteur*. Manguinhos, Oswaldo Cruz e a história da ciência no Brasil. Rio de Janeiro: FAPERJ/Relume Dumará.

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

Dear, P. (2001), "Science Studies as Epistemography", *in* Jay A. Labinger e Harry Collins (orgs.), *The One Culture? A Conversation about Science*. Chicago: University of Chicago Press, 128-141.

Dewey, J. (1977) [1908], "Does Reality Possess Practical Character?", *in The Middle Works*. Vol. 4. Carbondale: Southern Illinois University Press, 125-142.

Dewey, J. (1991a) [1938], "Logic: The Theory of Inquiry", *in The Later Works*. Vol.12. Carbondale: Southern Illinois University Press.

Dewey, J. (1991b) [1941], "Propositions, Warranted Assertibility, and Truth", *in The Later Works*. Vol. 14. Carbondale: Southern Illinois University Press, 168-188.

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

Eckart, W. U. (2002), "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 (1), 69-89.

European Helicobacter Study Group (1997), "Current European Concepts in the Management of Helicobacter pylori Infection. The Maastricht Consensus Report", *Gut*, 41, 8-13.

Figueiredo, C. (2000a), *vacA, cagA and iceA Genes of Helicobacter pylori: Genotyping, Epidemiology and Clinical Relevance*. Doctoral Dissertation. School of Medicine, University of Oporto.

Figueiredo, C. *et al.* (2000b), "Genetic organization and heterogeneity of the iceA locus of Helicobacter pylori", *Gene*, 246: 59-68.

Figura, N.; Bianciardi, L. (2002) "Helicobacters were discovered in Italy in 1892: An episode in the scientific life of an eclectic pathologist, Giului Bizzozero", in Barry Marshall (ed.), *Helicobacters Helicobacter Pioneers Firsthand accounts from the scientists who discovered helicobacters, 1892-1982*. Victoria, Australia: Blackwell Publishing, 1-13.

Fleck, L. (1979/1935), *Genesis and Development of a Scientific Fact*. Chicago: University of Chicago Press.

Fukuda, Y. *et al.* (2002), "Kasai, Kobayashi and Koch's postulates in the history of Helicobacter pylori", in Marshall (ed.), *Helicobacters Helicobacter Pioneers Firsthand accounts from the scientists who discovered helicobacters, 1892-1982*. Victoria, Australia: Blackwell Publishing, 15-24.

Fuller, S. (2000), *Thomas Khun: A Philosophical Tale for Our Times*. Chicago: University of Chicago Press.

Geison, G. L. (1995), *The Private Science of Louis Pasteur*. Princeton: Princeton University Press.

Geison, G. L. (2002), "Organization, Products, and Marketing in Pasteur's Scientific Enterprise", *History and Philosophy of the Life Sciences*, 24 (1), 37-51.

Geison, G. L.; Laublicher, M. D. (2001), "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, 1-29.

Gieryn, T. F. (1999), *Cultural Boundaries of Science: Credibility on the Line*. Chicago: University of Chicago Press.

Gilbert, N.; Mulkay, M. (1984), *Opening Pandora's Box: A Sociological Analysis of Scientists' Discourse*. Cambridge: Cambridge University Press.

Goodwin, C. S. (1994), "How Helicobacter pylori acquired its name, and how it overcomes gastric defense mechanisms", *Journal of Gastroenterology and Hepatology*, 9 (Supplement 1): S1-S3.

Graham, D. (2006), "Helicobacter 2006: A Note from the Editor", *Helicobacter*, 11, 1.

Hacking, I. (2002), *The Historical Ontology*. Cambridge, MA: Harvard University Press.

Haraway, D. J. (1991), *Simians, Cyborgs and Women: The Reinvention of Nature*. London: Free Association Books.

Haraway, D. J. (1997), *Modest_Witness@Second_Millenium.FemaleMan©_Meets_Oncomouse™: Feminism and Technoscience*. New York: Routledge.

Harding, S. (2004) (org.), *The Feminist Standpoint Theory Reader: Intellectual and Political Controversies.* New York: Routledge.

Haskins, C.; Seiple, D. I. (1999), *Dewey Reconfigured: Essays on Deweyan Pragmatism*. Albany: State University of New York Press.

Hickman, L. A. (2001), *Philosophical Tools for Technological Culture: Putting Pragmatism to Work*. Bloomington: Indian University Press.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (1994), *Schistosomes, liver flukes and Helicobacter pylori, IARC Monograph on the Evaluation of Carcinogenic Risks to Humans*, 61: 1-241.

Keating, P.; Cambrosio, A. (2003), *Biomedical Platforms: Realigning the Normal and the Pathological in Late Twentieth-Century Medicine*. Cambridge, Massachusetts: MIT Press.

Keller, E. F.; Longino, H. (1996) (orgs.), *Feminism and Science*. Oxford: Oxford University Press.

Kevles, D. J.; Hood, L. (1992) (eds.), *The Code of Codes: Scientific and Social Issues in the Human Genome Project.* Cambridge, Massachusetts: Harvard University Press.

Knorr-Cetina, K. D. (1981), *The Manufacture of Knowledge: An Essay on the Constructivist and Contextual nature of Science*. Oxford: Pergamon Press.

Langenberg, M.-L. *et al*. (1984) "Campylobacter-Like Organisms in the Stomach of Patients and Healthy Individuals", *The Lancet*, 16 June: 1348.

Latour, B. (1987), *Science in Action: How to Follow Scientist and Engineers through Society*. Milton Keynes: Open University Press.

Latour, B. (1988), *The Pasteurization of France*. Cambridge, Massachusetts: Harvard University Press.

Latour, B. (1991), *Nous n'avons jamais été modernes*. Paris: La Découverte.

Latour, B. (1996), *Petite réflexion sur le culte moderne des dieux faitiches*. Paris: Les Empêcheurs de penser en rond.

Latour, B. (1999), *Pandora's Hope: Essays on the Reality of Science Studies*. Cambridge, Massachusetts: Harvard University Press.

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

Latour, B.; Woolgar, S. (1986), *Laboratory Life: The Construction of Scientific Facts*. Princeton: Princeton University Press (2sd edition revised).

Lawrence, C.; Shapin, S. (1992) (eds.), *Science Incarnated*. Chicago: University of Chicago Press.

Longino, H. (1990), *Science as Social Knowledge: Values and Objectivity in Scientific Inquiry*. Princeton: Princeton University Press.

Longino, H. (2002), *The Fate of Knowledge*. Princeton: Princeton University Press.

Löwy, I. (2001), *Virus, moustiques et modernité: La fièvre jaune au Brésil entre science et politique*. Paris: Éditions des Archives Contemporaines.

Lynch, M. (1982), "Technical Work and Critical Inquiry: Investigations in a Scientific Laboratory", *Social Studies of Science*, 12, 499-533.

Lynch, M. (1985), *Art and Artifact in Laboratory Science*. London: Routledge and Kegan Paul.

Lynch, M. (1993), *Scientific Practice and Ordinary Action: Ethnomethodology and Social Studies of Science*. Cambridge: Cambridge University Press.

Malfertheiner, P., *et al.* (2002), "Current Concepts in the Management of Helicobacter pylori Infection. The Maastricht 2-2000 Consensus Report", *Alimentary Pharmacology and Therapeutics*, 16, 167-180.

Malfertheiner, P. *et al*. (2005), "Guidelines for the management of Helicobacter Pylori infection – Summary of the Maastricht- 3 2005 Consensus Report", *Business Briefing: European Gastroenterology Review*, 59-60, 998-999.

Marshall, B. (2002) (ed.), *Helicobacter Pioneers: Firsthand Accounts from the Scientists Who Discovered Helicobacters, 1892-1982.* Victoria, Australia: Blackwell Publishing.

Marshall, B. (2002a) "Preface", in Marshall B. (ed.), *Helicobacter Pioneers: Firsthand Accounts from the Scientists Who Discovered Helicobacters, 1892-1982.* Victoria, Australia: Blackwell Publishing xi-xii.

Marshall, B. (2002b) "The discovery that Helicobacter pylori, a spiral bacterium, caused peptic ulcer disease", in Marshall B. (ed.), *Helicobacter Pioneers: Firsthand Accounts from the Scientists Who Discovered Helicobacters, 1892-1982.* Victoria, Australia: Blackwell Publishing, 165-202.

Marshall, B. J. (1983), "Letter. Unidentified Curved Bacilli on the Gastric Epithelium in Active Chronic Gastritis", *The Lancet*, 4 June, 1273-1275.

Marshall, B. J.; McGechie, D. B.; Armstrong, J. A. (1985), "Attempt to Fulfill Koch's Postulates for Pyloric Campylobacter", *The Medical Journal of Australia*, 142: 436-439.

Marshall, B. J.; Warren, J. R. (1984), "Unidentified Curved Bacilli in the Stomach of Patients with Gastritis and Peptic Ulceration", *The Lancet*, 16 June, 1311-1314.

McNulty, C.A.M.; Watson, D.M. (1984) "Spiral Bacteria of the Gastric Antrum", *The Lancet*, May 12, 1068-1069.

Medawar, P. (1996), "Is the Scientific Article a Fraud?", in *The Strange Case of the Spotted Mice and Other Classic Essays on Science*. Oxford: Oxford University Press.

Mégraud, F. (2007) "Evolution of Helicobacter pylori Research as Observed through the Workshops of the European Helicobacter Study Group", *Helicobacter*, 12 (Suppl. 2), 1-5.

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

Modlin, I.M. (2002) "Foreword", in Marshall B. (ed.), *Helicobacter Pioneers: Firsthand Accounts from the Scientists Who Discovered Helicobacters, 1892-1982.* Victoria, Australia: Blackwell Publishing, vii-x.

Mol, A. (2002), *The Body Multiple: Ontology in Medical Practice*. Durham, North Carolina: Duke University Press.

Morris, A.; Nicholson, G. (1987) "Ingestion of Campylobacter pyloridis causes gastritis and raised fasting gastric pH", *American Journal of Gastroenterology*, 82, 192-199.

Myers, G. (1990), *Writing Biology: Texts in the Social Construction of Scientific Knowledge*. Madison, Wisconsin: University of Wisconsin Press.

Nunes, J. A. (2004), "Do 'nome das acções' ao 'nome das coisas': crenças e produção de objectos epistémicos nas ciências da vida e na biomedicina", in F. Gil, P. Livet and J. P. Cabral (eds.), *O processo da crença*. Lisbon: Gradiva, 402-412.

Nunes, J. A. (2008), "O resgate da espistemologia", *Revista Crítica de Ciências Sociais*, 80, 45-70.

Osler, W.; MacRae, T. (1920), *Principles and Practice of Medicine*. New York: Appleton.

Palmer, E.D. (1954) "Investigation of the Gastric Mucosa Spirochetes of the Human", *Gastroenterology*, 27 (2), 218-220.

Parker, J.; Parker, P. (2004) (Ed.), *The Official Patient's Sourcebook on H.p. Infection*. San Diego: ICON Health Publications.

Peirce, C. S. (1992), *The Essential Peirce*. Bloomington: Indiana University Press.

Petryna, A. (2002), *Life Exposed: Biological Citizens after Chernobyl*. Princeton: Princeton University Press.

Phillips, A.D. *et al.* (1984) "Gastric Spiral Bacteria". *The Lancet*, 14 July, 100-101.

Pinch, T. (1985), "Towards an Analysis of Scientific Observation: The Externality and Evidential Significance of Observational Reports in Physics", *Social Studies of Science*, 15, 3-36.

Pratt, S. L. (2002), *Native Pragmatism: Rethinking the Roots of American Philosophy*. Bloomington: Indiana University Press.

Rabinow, P. (1996), *Making PCR: A Story of Biotechnology*. Chicago: University of Chicago Press.

Rabinow, P. (2003), *Anthropos Today: Reflections on Modern Equipment*. Princeton: Princeton University Press.

Rabinow, P. (2008), *Marking Time: On the Anthropology of the Contemporary*. Princeton: Princeton University Press.

Rabinow, P.; Dan-Cohen, T. (2005), *A Machine to Make a Future: Biotech Chronicles*. Princeton: Princeton University Press.

Rasmussen, N. (1997), *Picture Control: The Electron Microscope and the Transformation of Biology in America, 1940-1960*. Stanford: Stanford University Press.

Rheinberger, H.-J. (1997), *Toward a History of Epistemic Things: Synthesizing Proteins in the Test Tube*. Stanford: Stanford University Press.

Romaniuc, P.J. *et al.* (1987) "Campylobacter pylori, the Spiral Bacterium Associated with Human Gastritis, Is Not a True Campylobacter sp", *Journal of Bacteriology*, 2137-2141.

Rouse, J. (1996a), "Beyond Epistemic Sovereignty", in Peter Galison and David J. Stump (orgs.), *The Disunity of Science: Boundaries, Contexts, and Power*. Stanford: Stanford University Press, 398-416

Rouse, J. (1996b), *Engaging Science: How to Understand its Practices Philosophically.* Ithaca: Cornell University Press.

Rouse, J. (2002), *How Scientific Practices Matter: Reclaiming Philosophical Naturalism*. Chicago: University of Chicago Press.

Rouse, J. (2004), "Barad's Feminist Naturalism", *Hypathia*, 19 (1), 142-161.

Santos, B. S. (2007) (org.), *Cognitive Justice in a Global World: Prudent Knowledges for a Decent Life*. Lanham: Lexington Books.

Schiebinger, L. (1999), *Has Feminism Changed Science?* Cambridge, Massachusetts: Harvard University Press.

Selzer, J. (1993) (org.), *Understanding Scientific Prose*. Madison: University of Wisconsin Press.

Shapin, S.; Schaffer, S. (1985), *Leviathan and the Air Pump: Hobbes, Boyle, and the Experimental Life.* Princeton: Princeton University Press.

Shousha, S. *et al* (1984) "Gastric Spiral Bacteria", *The Lancet*, 14 July: 101.

Stengers, I. (1996), *Cosmopolitiques. Tome 1. La guerre des sciences*. Paris: La Découverte/Les Empêcheurs de penser en rond.

Stengers, I.; Bensaude-Vincent, B. (2003), *100 mots pour commencer à penser les sciences.* Paris: Les Empêcheurs de Penser en Rond.

Talbot, J. A. (1970), *A Biographical History of Medicine: Excerpts and Essays on the Men and their Work*. New York: Grune and Stratton.

Taylor, P. J. (2008), *Agency, Structuredness, and the Production of Knowledge within Intersecting Processes*. Chicago: University of Chicago Press.

Thagard, P. (1998a), "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, 107-136.

Thagard, P. (1998b), "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, 317-342.

Thagard, P. (1999), *How Scientists Explain Disease*. Princeton, New Jersey: Princeton University Press.

Thomas, J.M. et al (1984) "Gastric Spiral Bacteria", *The Lancet*, 14 July, 100.

Tomb, J.F. *et al.* (1997), "The Complete Genome Sequence of the Gastric Pathogen Helicobacter pylori", *Nature*, 388, 539-547.

van Doorn, L.J. *et al.* (1998a), "Typing of Helicobacter pylori vacA gene and detection of cagA gene by PCR and reverse hybridisation", *Journal of Clinical Microbiology*, 36, 1271-1276.

van Doorn, L.J. *et al.* (1998b), "Expanding allelic diversity of Helicobacter pylori vacA", *Journal of Clinical Microbiology*, 36, 2597-2603.

van Doorn, L.J. *et al.* (1998c), "Clinical relevance of the cagA, vacA and iceA status of Helicobacter pylori", *Gastroenterology*, 115, 58-66.

van Doorn, L.J. *et al.* (1999a), "Distinct variants of Helicobacter pylori cagA are associated with vacA subtypes", *Journal of Clinical Microbiology*, 37, 2306-2311.

van Doorn, L.J. *et al.* (1999b), "Geographic distribution of vacA allelic types of Helicobacter pylori", *Gastroenterology*, 116, 823-830.

Warren, J. R. (1983), "Unidentified Curved Bacilli on Gastric Epithelium in Active Chronic Gastritis", *The Lancet*, 4 June, 1273.

Warren, J.R. (2002) "The discovery of Helicobacter pylori in Perth, Western Australia", Marshall B. (ed.), *Helicobacter Pioneers: Firsthand Accounts from the Scientists Who Discovered Helicobacters, 1892-1982.* Victoria, Australia: Blackwell Publishing, 151-164.

West, C. (1989), *The American Evasion of Philosophy: A Genealogy of Pragmatism*. Madison: University of Wisconsin Press.

Woolgar, S. (1976), "Writing an Intellectual History of a Scientific Development: The Use of Discovery Accounts", *Social Studies of Science*, 6, 395-422.

Woolgar, S. (1980), "Discovery: Logic and Sequence in a Scientific Text", in K. Knorr, R. Krohn e R. Whitley (orgs.), *The Social Process of Scientific Investigation. Sociology of the Sciences Yearbook.* Vol. IV. Dordrecht: D. Reidel, 239-268.

Worboys, M. (2000), *Spreading Germs: Disease Theories and Medical Practice in Britain, 1865-1900*. Cambridge: Cambridge University Press.

Yamada, T. (1994), "NIH Consensus Conference. Helicobacter pylori in Peptic Ulcer Disease", *JAMA- Journal of the American Medical Association*, 272, 65-69.

Centro de Estudos Sociais
Laboratório Associado
Universidade de Coimbra

A Cescontexto é uma publicação online de resultados de investigação e de eventos científicos realizados pelo Centro de Estudos Sociais (CES) ou em que o CES foi parceiro. A Cescontexto tem duas linhas de edição com orientações distintas: a linha "Estudos", que se destina à publicação de relatórios de investigação e a linha "Debates", orientada para a memória escrita de eventos.

CES
Colégio de S. Jerónimo
Apartado 3087
3001-401 Coimbra, Portugal
T. +351 239 855 570
F. +351 239 855 589
www.ces.uc.pt
ces@ces.uc.pt

CES - Lisboa
Picoas Plaza
Rua do Viriato, 13
Lj 117/118
1050-227 Lisboa, Portugal
T. +351 216 012 848
F. +351 216 012 847
www.ces.uc.pt/ces-lisboa
ceslx@ces.uc.pt

· U C ·
COMPETE
QREN QUADRO DE REFERÊNCIA ESTRATÉGICO NACIONAL
UNIÃO EUROPEIA FEDER
FCT Fundação para a Ciência e a Tecnologia
POPH