Historical Epistemology of the Concept of Virulence:

Molecular, Ecological, and Evolutionary Perspectives on Emerging Infectious Diseases in the 19th and 20th Century

Thesis submitted by Pierre-Olivier Méthot to the University of Exeter and the Université Panthéon-Sorbonne (Paris1) as a thesis for the degree of Doctor of Philosophy in philosophy, December 2011.

I certify that all material which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this of any other University.

Pierre-Olivier Méthot

PREFACE

Writing a Ph.D. thesis was for me an intrinsically social enterprise. During my doctoral studies I have met countless extraordinary individuals who have helped me, in various ways, put together certain ideas and concepts and, without whom, this body of work would not have existed, at least not in its current form.

The seven chapters collected in this dissertation, titled *Historical Epistemology of the Concept of Virulence: Molecular, Ecological, and Evolutionary Aspects of Emerging Infectious Diseases in the nineteenth and twentieth Century*, were drafted and completed at different times and places over the past four years. They reflect both the author's own hesitations and certitudes about the topic but also the conviction that a wholly integrated approach in the history and philosophy of the life sciences is a desirable goal to be pursued.

Upon arriving in Exeter, after completing a bachelor's and a master's degree in philosophy at the Université de Montréal, the latter on the topic of biological individuality, I decided to concentrate on problems in the philosophy of medicine, informed by contemporary philosophy of biology. A natural direction was to explore the field of evolutionary medicine and the consequences of different conceptions of the evolution of pathogens' virulence for current medical understanding of health and disease. Endeavouring to approach these problems from an integrated history and philosophy of science perspective, the work of Georges Canguilhem as well as that of Ian Hacking and Hans-Jörg Rheinberger was particularly attractive and useful for developing a conceptually rich framework.

One of the main challenges, however, was to strike the right balance between critically examining aspects of the methodological approach developed by Canguilhem, while at the same time addressing some of the philosophical issues raised by recent advances in biomedicine. In other words, the task I set myself was to combine in-depth analyses of an author's methodology with historic-philosophical work on a concept, that is, on a problem.

ACKNOWLEDGEMENTS

The present work was supervised by three directors and two mentors and was written in three different academic institutions located in three different countries. I would like to say a few words about how it all happened.

I first came to Exeter in September 2007 to undertake a Ph.D. in the history and philosophy of biology under the supervision of John Dupré, whom I want to thank as warmly as possible for welcoming me as a doctoral student at Egenis. During those years, John was extraordinarily encouraging and supportive of my several, sometimes embryonic doctoral projects (and versions thereof). He is a wonderful supervisor, and I am most thankful to him for providing me with the academic freedom I needed to pursue my research interests, combined with a critical but always constructive evaluation of my written work.

Throughout my first year in Exeter I made the decision to study in more depth the philosophy of Canguilhem, and upon a suggestion from Staffan Müller-Wille, I contacted Jean Gayon who helped me set up a *cotutelle* agreement between the University of Exeter and the Institut d'histoire et de philosophie des sciences et des techniques (IHPST) at Université Paris1 (Panthéon-Sorbonne), and to whom I am extremely grateful for accepting to become my supervisor. I am indebted to Jean Gayon for many reasons, not the least for his careful reading (and re-reading) of the several drafts of articles and chapters I sent him over the years but also for his instruction in the history and philosophy of biology. Always providing me with sound advice, he also was a reassuring presence in the academic jungle of Paris.

Following my upgrade exam in 2009, as I wanted to give a sharper historical angle to my research, it was then decided that Staffan would also supervise my work, a decision about which I was most thankful from the outset. Over the past four years, Staffan provided me with a number of perspectives in the history and epistemology of the life sciences as well as constant encouragement, productive feedback and, I must say, inspiration. I am also grateful to him for helping me to think in terms of "concepts in action".

Additionally, as a Ph.D. student, I completed two research stays at IHPST in Paris: the first one between September 2008 and January 2009 and the second one between January and June 2010. I would like to thank my friends and colleagues at the IHPST, ENS, and the Maison des Étudiants Canadiens – Alexandra Bacopoulos-Viau, Élodie Baget, Steeves Demazeux, Isabelle Drouet, Vincent Grondin, Lara Kutschenko, Johannes Martens, Francesca Merlin, Antonine Nicoglou, Dave Savard, and Frédérique Théry without whom my time in Paris (especially at the BIUM) would have been much less enjoyable.

I would also be remiss if I did not mention Camille Limoges here. Working alongside him at the CAPHES, on rue d'Ulm, was one of the intellectual highlights of my stays in Paris, and I would like to thank him for his useful advice and his encyclopaedic knowledge of Canguilhem's philosophy and history.

In Exeter, I have had the opportunity of knowing two mentors: Maureen O'Malley (now in Sydney) and Lenny Moss. I would like to thank each of them, not only for their constant support throughout the years but also for sharing their extensive knowledge in microbiology and hiking, and continental philosophy, respectively.

During 2008, I was extremely lucky to land at 16 Morley Road, where many philosophers and sociologists in Exeter have since spent some time. This place that I have come to call home will never be forgotten. My dear Morley-Road Friends, I look forward to seeing you all again soon. Many thanks to Daniele Carrieri, Valeria Cinaglia, Mattia Gallotti, Sam Jones, and Hadeel Maaitah for those fabulous years spent in your company.

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From August until the end of October 2011, I was a visiting researcher at the Brocher Foundation, located on the shore of Lake Geneva in Hermance, Switzerland, where I completed the first draft of the present work. For their support, kindness, Frisbee-throwing sessions, conversations, and more, I would like to thank all my fellow Brocher researchers, and in particular Haidan Chen, Nouzha Guessous, Carl Power, John Rasko, Leigh Rich, Mansooreh Saniei, Gail van Norman, Esther van Zimmeren, and Lorna Weir, in addition to all of the foundation's staff for making this place unique in the world.

There are many other people I wish to thank for being there all those years and for providing feedback, encouragement, and/or teaching at different points: Samuel Alizon, Rachel Ankeny, Frédéric Bouchard, Matteo Borri, Havi Carel, Teresa Castelão-Lawless, Hasok Chang, Bernardino Fantini, Uljana Feest, Élodie Giroux, Paul Griffiths, Philippe Huneman, Andrew Mendelsohn, Michel Morange, Thomas Pradeu, Julian Reiss, Hans-Jörg Rheinberger, Neeraja Saankaran, Marc Silberstein, Bruno Strasser, and Charles Wolfe. Alex, Leigh, and Neeraja's editing skills saved me from a number of mistakes in the last stages of writing-up and I am very thankful to them for that. All remaining errors are, of course, mine. I also want to acknowledge the continual long-distance support of my dear, old friends, Dominique Drouin, Patrick Gagné, Rebecca Graf, Alexandre Lapointe, Francesco Lopes, and Fannie Valois-Nadeau, some of whom I had the pleasure to welcome in Exeter a few times or meet elsewhere in Europe. I would also like to extend my thanks to Hexi without whom, it is fair to say, I would probably not have gone on to study in Exeter in the first place.

At this point, I should like to acknowledge the generous financial support of the Social Sciences and Humanities Research Council of Canada (752-2007-1257), Egenis, the Université Paris 1 (Panthéon-Sorbonne), and the Brocher Foundation.

The final word was written in yet another country. Back in Montréal, after my Brocher residency, I devoted the last month to complete the work and translate it into French. I would like to thank my sisters, Mireille and Catherine, and my parents, Hugues and Marcelle, to whom this work is dedicated, as warmly as possible for their love during the past 31 years and for their unwavering support in those last weeks of intense writing and editing. Merci !

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AUTHOR'S DECLARATION

One paragrah of the introduction in the section titled "Towards a more inclusive history and philosophy of the life sciences", is taken from Méthot et al. (2011).

Several passages of the section titled "The category of 'experimental' in *The Normal and the Pathological*" in chapter 1 are taken from Méthot (2009a).

Chapter 2 is a revised and combined version of Méthot (2011) and Méthot (2009b).

ABSTRACT

This thesis focuses on the trajectory of the biomedical concept of virulence from 1880 until the present. Following the concept across disciplinary boundaries, from a *longue durée* history perspective, it explores how virulence was shaped through two distinct, although sometimes overlapping, "styles of reasoning". Located at the intersection of several distinct research domains in biology and medicine, the concept of virulence provides, in addition, a window into the complex and changing relations between evolutionary biology and the health sciences (broadly construed) over the past two centuries. Moving back and forth between field experiments and the laboratory, this work examines, through the lens of historical epistemology, the emergence of what I call the molecular and the ecological styles, and their respective conceptual practices. It focuses on the ways in which these styles operationalize the distinction between virulent or avirulent organisms in sometimes opposite sense: Whereas in the molecular (or endogenous) style the expression of virulence is explained by properties of internal structures of the infectious agent (e.g. polysaccharide capsule, virulence gene, or pathogenicity island), the concept of virulence in the ecological (or exogenous) style reflects, in contrast, either a lack of adaptation between two species (avirulence hypothesis) or the existence of one or more ecological compromises between, say, the mode of transmission of a pathogen and its host's recovery rate (trade-off model). Both styles can be said to originate in the medical bacteriology of the late-nineteenth century, but while the former grew mostly out of the work of Louis Pasteur and Robert Koch in Europe, the latter was primarily shaped by Theobald Smith in the United States. Nearly a century later, the introduction of the category of emerging infectious disease within public health discourses in the mid-1990s facilitated a rapprochement between the two styles that had, so far, remained apart. Employing the 1918–1919 influenza pandemic as an example in which to illustrate the trajectory of the molecular and the ecological approaches, the diversity of explanatory schemes developed to account for the pandemic's exceptional virulence points toward an unresolved, and yet productive, epistemic tension between the two styles, on the one hand, and the intrinsic polarity of the concept of virulence itself, on the other.

Keywords: Disease, evolution, parasitism, bacteriology, ecology, operationalism, styles of reasoning.

For a biologist, there are two different ways of examining the history of his science. Firstly, it may be considered as a succession of ideas, thus involving a search for the thread which guided thought along the path to current theories. This is reverse history, so to speak, which moves back from the present towards the past. Step by step, the forerunner of the current hypothesis is chosen, then the forerunner of the forerunner, and so on [...]

The alternative approach to the history of biology involves the attempt to discover how objects become accessible to investigation thus permitting new fields of science to be developed. It requires analysis of the nature of these objects, and of the attitude of the investigators, their methods of observation, and the obstacles raised by their cultural background. The importance of a concept is defined operationally in terms of its role in directing observation and experience. There is no longer a more or less linear sequence of ideas, each produced from its predecessor, but instead a domain which thought strives to explore, where it seeks to establish order and attempts to construct a world of abstract relationships in harmony not only with observations and techniques, but also with current practices, values and interpretations.

François Jacob, 1970

À mes parents,

GENERAL INTRODUCTION

When the H5N1 influenza strain emerged in Asia in 1997 it triggered massive economic loss in poultry industry and caused, overall, less than 600 laboratory-confirmed cases in humans (although these were very deadly). A number of factors could explain why between-human transmission was relatively ineffective in this case and why the avian virus did not go pandemic in human populations. Some scientists think, for example, that only H1, H2, and H3 strains can cause influenza pandemic. Others, in turn, argue that in order to adapt to humans, the virus' genes would first have to reasort, that is, to reshuffle with those of a human variety, a process known as antigenic shift that usually takes place in pigs infected with both humans and avian strains (Enserink 2011). Yet, a recent study questions these and similar arguments and assumptions about the biology and evolution of influenza viruses. In effect, in late September 2011 the *New Scientist* magazine reported that Ron Fouchier, a Dutch virologist working at the Erasmus Medical Center, succesfully altered a strain of influenza (H5N1) rendering it airborne transmissible between mammals (ferrets, in this case). Using reverse genetics techniques, Fouchier first induced three mutations in two genes that allowed the avian virus to adapt (and thus infect) mammals. Using the mutated strain, he then artificially infected more ferrets by serial passages. After ten generations, the virus had mutated and had become airborne. With this newly acquired set of five genes healthy ferrets could contract the disease just by sitting in a cage next to a sick animal. As Fourrier said, these mutations are all found in nature but not in the same strain. In other words, the Dutch scientist had "given deadly flu virus wings" (Enserink 2011)

Historically, influenza viruses adapted to ferrets are also adapted to man, however. Because of this rather alarming possibility Fouchier's experiment, submitted for publication to *Science*, is now undergoing a safety review by the U.S. National Science Advisor Board for Biosecurity (NSABB), a National Institute of Health (NIH) advirsory panel.[1] Fouchier's work has spurred considerable debates within scientific communities and across social networks, both in Europe and in the U.S., regarding the dangers of dual-

[1] A similar research article produced by a U.S. team led by Yoshihiro Kawaoka at the University of Wisconsin-Madison, and submitted to *Nature*, is also under review by the NSABB.

use technologies amidst concerns that if relased (intentionally or not) the newly-created pathogen could trigger a deadly pandemic in human populations because it could spread much more effectively.[2] Head of the NSABB, microbiologist Paul Keim, was quoted in a short piece in *Science* saying "he can't think of another pathogenic organism as scary as this one" (Keim, quoted in Enserink 2011, 1193). Others like Fouchier, however, argue that this research should yield unexpected benefits from a public health standpoint because scientists will then be in a position to investigate the precise mutations that make this influenza strain particularly virulent, to develop appropriate counter-measures like vaccines, and to monitor future outbreaks more effectively.

At the time the present work went off to print, we still ignore what the NSABB's final decision will be.[3] In any case, the safety review board lacks the authority to prevent the publication of Fouchier's article. Beyond the problem of dual-use technology and the obstacles in developing a "culture of responsability" (NSABB 2011) in the life sciences, Fouchier's experiment reflects a strong reductionist tendency in present-day biomedicine. Indeed, his case is not isolated. A similar situation was brought to light in 2005 when a team of American scientists re-created the strain of the 1918-19 influenza pandemic, which claimed over forty millions of lives worldwide, as to whether their results and methods should be published. After a last-minute safety review from the NSABB the article was nonetheless published in *Science* (Tumpey et al. 2005) alongside the technique of how to re-create the 1918 strain. A note (added in proofs, as recommended by the NSABB) indicates the potential public health benefits this research is likely to create.

While researchers (and funding agencies) tend to strongly emphasize the need to investigate the smallest genetic or molecular components of viruses and bacteria, other

[2] The concept of dual-use technology refers to the potential for a new technology or object to be employed to achieve either well-intended or nefarious goals. Influenza research is the paradigm case of dual-use technology. See Rappert (2007); Selgelid (2005); and chapter 7.

[3] The decision came out on December twentieth 2011 – one day after this work was submitted for evaluation. The NSABB recommended censoring part of the methodology to decrease potential risks linked to biosecurity. In late January 2012, the scientific community agreed on a 60 days moratorium to study the potential impacts, both social and ethical, and from a public health perspective, of the work of Fouchier in the Netherlands and Kawaoka in the U.S. Amidst growing global controvery, the scientists who signed the declaration agreed not to pursue any work on highly pathogenic avian influenza H5N1 during this time period.

factors, including ecological and evolutionary processes, also impact on whether an infectious disease will turn pandemic or not, however. In other words, a mosaic of interconnected elements often partakes to the overall explanation of why a disease is deadly, or what can increase its virulence. The articulation of these elements in explaining changes in virulence, in addition to the complex and changing relations between evolutionary biology and medicine broadly construed, are central to the present project. Questions like "why do some diseases persist while others decline?" Or, "why was the 1918-19 influenza pandemic exceptionally virulent?" can benefit from evolutionary insights. From a *longue durée* history perspective, this thesis investigates the ways in which scientists have articulated evolutionary theory with various explanations of pathology from the late nineteenth century until the present, especially in the field of (emerging) infectious diseases.

EVOLUTION, HEALTH, AND DISEASE IN A "WORLD ON ALERT"

The collaboration of psychiatrist Randolph Nesse and evolutionary biologist George Williams during the 1980s culminated, twenty years ago, in the creation of "Darwinian medicine" (Williams and Nesse 1991), an offshoot of the adaptationist approach in evolutionary biology (Gammelgaard 2000). Two aspects of Darwinian medicine are especially noteworthy: firstly, when looked at from an evolutionary standpoint some diseases and symptoms (e.g. anxiety, depression, fever, iron depletion) are seen as providing a selective advantage to their bearers and are hence not to be treated as pathologies at all; secondly, because the environment in which we now live has dramatically changed, the nature of this selective advantage is much less obvious. Thus, there is often a mismatch between human physiology that evolved during the Pleistocene epoch and today's modern environments. This maladapted state, it is argued, increases the risks of diseases such as chronic illnesses, cancers, and so on.

While Darwinian medicine was useful in bringing to the attention of physicians some of the potential benefits of applying evolutionary thinking to the field, some underlying ideas of Darwinian medicine remain controversial (chapter 2). More importantly maybe, older connections between evolutionary biology and the health sciences were largely left

aside in favour of the development of adaptationist hypotheses about human's biological past. These trends in "evolutionary medicine", emphasize not so much how humans face new diseases because of the way our (normal) physiology has evolved during the Stone Age or Pleistocene era, but insist rather on the persistent, dynamic co-evolution of human populations and microorganisms, and explore how these relations between man and the microbial world shape states of health and disease. Recently, "virulence management" theorists have picked up the idea of using evolutionary theory to model the ways in which various human activities and social practices impinge on the delicate biological relations between microbes, and how this influences human health (Dieckmann et al. 2002).

This mathematical and ecological approach to virulence was developed almost at the same time governments and health authorities like the World Health Organization (WHO) recognized the burden of infectious diseases worldwide. Despite the recent steep rise in chronic and degenerative illnesses, infectious diseases still represent a global challenge for 21st century biomedicine, as they continue to claim 15 million lives annually (Morens, Folkers, and Fauci 2004). Scientists have now catalogued the emergence of 335 diseases in human populations between 1940 and 2004, the bulk of them emerging in the 1980s after rapid increase in drug resistance was detected (Jones et al. 2008). Microbial threats to human health are numerous and to make things worse virulent factors, drug resistance and receptor specificities vary widely among strains of the same species (Woolhouse and Antia 2008).[4] The evolutionary potential of microorganisms to undergo pathogenic change is, indeed, almost unlimited (Antolin 2009).

Changes in the environment and human behaviour can also dangerously tip the delicate balance established between man and microorganisms. As some have argued, humans may well be the "world's greatest evolutionary force" (Palumbi 2001) behind the increased virulence of pathogens as, through new practices, we are creating new routes for "viral traffic" (e.g. blood transfusion, organs transplantations); fostering behavioural changes facilitating pathogens' transmission (e.g. air travel, migrations, sexual practices, use of drugs, etc.); and introducing "new" pathogens from different parts of the world

[4] As Woolhouse and Antia (2008) pointed out human infections can be acquired from other humans; from animal reservoirs (zoonotic diseases); or from the wider environment (sapronose diseases).

into immunologically naive populations (Morse 1995). The emerging and re-emerging infectious diseases might be indicative of a third "epidemiologic transition" (Barrett et al. 1998; see Omran 1971). The latent potentiality of microorganisms to cause ill-health, as opposed to the view that the microbial world was largely static and fixed, was recently interpreted as nothing short of an "epistemological break" in the field of public health (Weir and Mykhalovskiy 2010, 62).

In the 1990s, the saying that "diseases know no borders" has become a cliché, and many recognized that a genuinely new approach to global public health was much needed (Roemer 1994, 421, quoted in Kings 2002, 62). In 1996, a WHO committee argued along the same lines that "no one is safe from infectious diseases" given that new ones are emerging, and previously conquered ones are returning:

> Far from being over, the struggle to control infectious diseases has become increasingly difficult. Diseases that seemed to be subdued, such as tuberculosis and malaria, are fighting back with increased ferocity. Some, such as cholera and yellow fever, are striking in regions once thought safe from them. Other infections are now so resistant to drugs that they are virtually intreatable. In addition, deadly new diseases such as Ebola hemorrhagic fever, for which there is no cure or vaccine, are emerging in many parts of the world. At the same time, the sinister role of hepatistis viruses and other infectious agents in the development of many types of cancer is becoming increasingly evident. The result amounts to a global crisis: no country is safe from infectious diseases. The socio-economic development of many countries is being crippled by the burden of these diseases. Much of the progress achieved in recent decades towards improving human health is now at risk (1996, 1, quoted in Van Loon 2002, 124).

This state of affairs, in the post-9/11 climate of the increased risks of bioterrorist attacks, culminated with newly elaborated International Health Regulations in 2005, approved by all 194 states members of the WHO. The new regulations emphasise the need for national and international collaboration in detecting, monitoring, and responding to disease outbreaks and emergence events in "hot spots" anywhere on the

planet.[5] Seen in this light, the (biomedical) world is truly "on alert" to use Weir and Mykhalovskiy's (2010) expression, and the saying attributed to the U.S. General Surgeon that it is time to close the book on infectious diseases (Stewart 1967) resonates today as being plainly wrong, and regrettable.[6] Yet, Stewart was not the only one to have this opinion. A few years before his alleged declaration, British anthropologist and epidemiologist Aidan Cockburn[7] wrote an influential book on *Evolution and Eradication of Infectious Diseases* (1963) where he made the famous statement that within one hundred years most human and animal diseases could be eradicated (Cockburn 1963). To those in the 1970s who voiced concerns regarding the possible resurgence of infections, the Australian immunologist and Nobel Prize winner Frank Macfarlane Burnet responded that although "there may be some wholly unexpected emergence of a new and dangerous infectious disease" we should expect "nothing of the sort that has marked the last fifty years" (Burnet and White 1972, 263). The eradication of smallpox in 1977 and the control of a number of other infectious and vector-borne diseases (e.g. malaria) supported these enthusiastic perspectives a step further (Snowden 2008).[8]

As analyzed in chapter 4, this view was supported by an influential and widespread evolutionary understanding of host, pathogens, and environmental interactions: the *avirulence hypothesis*. Promoted by the American bacteriologist Theobald Smith (1859-1934) this hypothesis considers that the "tendency of infectious diseases is toward a balanced parasitism" (Smith 1906, 1247). As a corollary, "mortality from infectious diseases would be greatly reduced through the operation of natural causes" (Smith 1904, 838). Smith recognized, however, that "how rapidly this evolution [towards avirulence]

[5] Surveillance is defined here as "the systematic ongoing collection, collation and analysis of data for public health purposes and the timely dissemination of public health information for assessment and public health response as necessary" (in Castillo-Salgado 2010, 95).

[6] The reference to Stewart's alleged statement, however, is almost never linked to a primary source, and the year of the quote varies from 1967 to 1969. While this quote may be a medical "urban myth" (Spellberg 2008), confirmation of the prevalence of such perspective during the 1960s and 1970s is given in Fauci (2005); Ewald (1994); see chapter 4.

[7] Cockburn was at the time was Assistant Commissioner of Health in Cincinnati (Ohio).

[8] In contrast, Thomas McKeown (1912-1988) defended the view that the decline in mortality from infectious diseases was well underway *before* the development of the medical model in the 1930s and 1940s. Socio-economic conditions (including public health measures and better living standards) therefore, and not medical progress alone, should be regarded as the genuine determinants of health.

may progress we have no means of knowing" (Smith 1921, 6). The possibility of eradicating diseases like smallpox, combined with the belief that evolution was going to naturally wipe out infections worked together in entertaining the possibility that infectious diseases would soon vanish, as population ecologist Richard Levins once pointed out (Levins 1994). But during the early 1980s the avirulence hypothesis and its corollary were *empirically* challenged following the augmentation of drug resistance worldwide, the beginnings of the AIDS pandemic, and the increase in emerging infections. Both were also *theoretically* challenged after the development of the trade-off model by evolutionary ecologists. Other work in medical bacteriology, bacterial genetics, and more recently, pathogenomics, has also contributed to downplay the latent optimism of the avirulence model.

THE CONCEPT OF VIRULENCE AND EMERGING INFECTIOUS DISEASES

The concept of virulence is central to a number of medical disciplines but is also often used by ecologists working on host-pathogens' relations and by evolutionary biologists. In medicine the concept is often invoked to characterize the severity of a disease in a patient, or to describe the scale of the damage caused by an epidemic in a population. Comparing levels of virulence between epidemics (population), or patients (individual) is only possible, however, once clear operational criteria have been established by practitioners. In the modern history of infectious disease, starting with the bacteriological revolution at the end of the nineteenth century, host death remains one of the most widely-used measures to quantify and assess virulence, although other methods have since been developed, drawing on new tools (LD_{50} test)[9] and concepts such as pathogenicity islands, virulence genes, or the trade-off model in epidemiology.

Coming from the latin *virulentus* (meaning "full of poison") this old medical term conjures-up images of disease and contagion, bringing to the fore cognate concepts such as epidemic, infection, pestilence and the like. Public health practitioners frequently classify one disease being more virulent than another or as gaining (or losing) virulence

[9] This test refers to the dose of, for instance, a virus that can kill at least 50% of the individuals to which it was inoculate. This test was developed in the early 1920s.

power over time. The decline in virulence observed in myxoma virus among rabbit population in Australia during the 1950s and 1960s is often cited as a case in point (Fenner and Radcliffe 1965). In contrast, the level of virulence of the influenza virus increased dramatically during the 1918-19 influena, claiming more victims than the Great War itself (McNeil 1976). Likewise, biomedical scientists frequently debate existing definitions of virulence and related terms like pathogenicity but no general definition has yet surfaced across (even within) disciplines concerned with the problem of infectious diseases. The concept of virulence is wholly disunified although it was and continues to be, of central epistemic importance for the medical sciences broadly construed. Yet, in contrast with other key biomedical categories capable of several (sometimes conflicting) interpretations like gene, species or organism, the concept of virulence has not received much attention from either philosophers or historians of science until recently (but see Mendelsohn 1998; 2002).

TWO WAYS OF UNDERSTANDING VIRULENCE

What is virulence? Virulence does not refer directly to a material or physical structure, although it relates to them in multiple ways. Virulence is in fact a process which, for many, refers to the capacity of a pathogen to successfully invade a host, reproduce, multiply and be transmitted to another host. According to this view, virulence is primarily the side-effect of complex, and perhaps incompletely or imperfectly evolved, life-cycles. For others, virulence correlates with toxins produced by pathogens or with their capacity to neutralize, manipulate, or evade the host's immunity, thanks to specific physiological traits like a polysaccharide capsule or a plasmid. Virulence, as Pastorian Émile Roux once said, is "the ability [of a pathogen] to live within an organism and exude poisons" (quoted in Nicolle 1939, 65). But if virulence is irreducible to a particular material substrate like a DNA sequence or a protein (e.g. HA and NA in influenza A viruses), the level of virulence has, in the wake of molecular biology, genomics, and synthetic biology, become increasingly associated with gene functions and other intra-cellular pieces. One of the functions of virulence genes is to facilitate the pathogen's entrance into a host or its transmission to new hosts. It is now common in molecular

pathology to link the level of virulence of a pathogen with its mobile elements (e.g. transposon, plasmids, and pathogenicity islands).

Yet immunologists and evolutionary ecologists might want to disagree with the view that virulence can be defined one-sidedly, i.e. without taking into account the overall reactions of the organism being infected by a pathogen, and the ecological context in which infection takes place. For these scientists, virulence refers to the *process* of infection as much as to the *infective properties* of either the host or the pathogen. Moreover, this propensity to cause severe disease is subject to selective forces and can therefore evolve in many, and sometimes unpredictable, ways (Ebert 1999). Here lies one of the difficulties and the (irreducible) tension in studying the phenomenon of virulence across the biomedical sciences: one can either look for determinants of pathogenic power analytically, that is from within microorganisms, or synthetically at the level of host-pathogen interactions in a given ecological environment. Each level of analysis has its own ways of characterizing the nature and causes of virulence, leading to the development of different measures to prevent or to treat infectious diseases. In effect, while ecological approaches contributed to the establishment of national and international programmes intended to increase detection and surveillance in emerging infections on a global scale, monitoring changes in virulence to prevent pandemics worldwide, molecular approaches facilitated the development of biomedical tools, such as vaccines or antibiotics, to fight infectious diseases either by reducing their pathogenic power, and/or by enhancing individual and group immunity.

These two ways of investigating the nature of virulence and pathogenicity have both a long history which is reflected in the divergent methods and objects of bacteriology, immunology, ecology and public health. In order to gain insight into these sometimes overlapping methodological and epistemological differences, the bulk of this dissertation concentrates on these two broad ways of understanding and explaining the evolution of virulence in the biomedical sciences. Building on a variation of this approach, and influenced by Ludwig Fleck, historian of science Ton van Helvoort traced the history of the modern concept of virus and the establishment of virology as a full-fledged autonomous discipline during the first half of the twentieth century (1994; 1993; 1992). According to him, the explanation of the nature of bacteriophagy swung back and forth between the

thought that bacteriophages are autonomous viruses, that is, “exogenous agents”, and the possibility that bacteriophages are, from an endogenous perspective, “the result of a derangement of the physiology of the bacterium” (1994, 98). For van Helvoort, there was a “clash” between research styles that took place in the 1950s and 1960s (1992, 572). In this thesis, I expand on the work of van Helvoort and I show that his initial distinction between exogenous and endogenous can usefully be applied to a number of fields outside virology. Adopting the Fleckian terminology of van Helvoort (1993), I label these perspectives the *exogenous* and the *endogenous* “thought-styles” – or “styles of reasoning” – as one focuses on the internal properties of disease-causing organisms (endogenous) while the other concentrates on the larger ecological context (exogenous). Viewing this distinction between the endogenous and the exogenous from a still broader perspective, one can see that it captures, and reformulates, an older distinction in the history of medicine between the ontological and the physiological views of disease. Whereas the former models diseases as invading agents coming from outside, the latter frames illnesses in terms of internal metabolic perturbations (see Temkin 1977).

In contrast with van Helvoort’s argument, however, my analyses reveal not a direct clash between research styles but rather, most of the time at least, a polite ignorance of one another, akin to the development of evolutionary biology and physiology in the late nineteenth century and well into the twentieth century. I argue that the exogenous and endogenous styles have developed along broad parallel lines through several (sometimes unrelated) disciplines, and that this divide has crossed the past century. Both styles can be said to originate in the medical bacteriology of the late-nineteenth century, but while the former grew mostly out of the work of Louis Pasteur and Robert Koch in Europe, the latter was primarily shaped by Theobald Smith in the United States. Nearly a century later, the introduction of the category of emerging disease within public health discourses in the mid-1990s facilitated a rapprochement and a dialogue between the two styles that had, so far, remained apart. Employing the 1918–1919 influenza pandemic as an example in which to illustrate the evolution of the molecular and the ecological approaches, the diversity of explanatory schemes developed to account for the pandemic’s exceptional virulence points toward an unresolved, and yet productive, epistemic tension between

the two styles, on the one hand, and the intrinsic polarity of the concept of virulence itself, on the other.

The evolutionary biologist Ernst Mayr has long suggested that functional and evolutionary approaches in biology lack unification (Mayr 1961). Another significant divide is between ecological and functional approaches. In this dissertation, I will show that recent work on the nature and mechanism of infection is starting to bridge these gaps between functional biology, ecology, and evolutionary biology. For example, in the case of the 1918 pandemic, both molecular and ecological approaches are thoroughly engaged in an evolutionary understanding of the pandemic, although each of them picks out a different aspect of what a Darwinian (or evolutionary) explanation consists of. Whereas ecological approaches focus on selective pressures (e.g. population density) acting on the hosts and the pathogen, molecular pathologists trace the evolutionary pathway of the influenza virus from animal(s) to man. In other words, the former analyses one of the main *mechanisms* of evolution – natural selection – while the latter describes the *path* of evolution – phylogeny –, to use Ruse's vocabulary (1992). Both aspects – that all livings things (including viruses and bacteria), through common descent, can be represented on a larger Tree of life diagram (increasingly becoming network-like), and that natural selection provides an explanation for those changes – are two of the most fundamental claims of the theory of evolution by natural selection, as developed by Charles Darwin in *On the Origin of Species* (1859).

ON THE CATEGORY OF STYLE IN THE HISTORY OF SCIENCE

Science is not understood (anymore) as a single, unified enterprise seeking to unveil the secrets of Nature through the steady progressive discovery of universal laws. Since twenty years, historians and philosophers have described how the different branches of the sciences are plural and genuinely disunified in both their epistemology and methodology (Galison and Stump 1996; Dupré 1993). In an attempt to capture significant aspects of how scientists investigate and carve out objects in the natural world, the historian of science Alistair Crombie has described the emergence of six styles of "scientific reasoning" in the history of Western science (1994). These styles are

"postulation"; "experimental"; "modeling"; "taxonomy"; "probabilistic and statistical analysis"; and "historical derivation" (Crombie, 1994). It is, however, the philosopher of science Ian Hacking (1992) who most clearly articulated the notion of "styles of reasoning" as being self-vindicating, autonomous scientific methods. Combining the experimental and probabilistic styles as defined by Crombie, Hacking introduced and investigated the "laboratory style" (Hacking 1992b).[10]

A rapid survey of the history and philosophy of science of the past fifty years indicates that there are many kindred notions available to characterize particular ways of doing and thinking about science. I do not aim to be exhaustive here but these include the concepts of "paradigm" (Kuhn 1962); "thought-style" (Fleck 1939); "research traditions" (Laudan 1988); "epistemic styles" (Maienschein 1991); "styles of scientific reasoning" (Hacking 1992); "styles of scientific thinking" (Crombie 1994); "scenes of inquiry" (Jardine 2000); "ways of knowing" (Pickstone 2004); as well as a number of other accounts (Elwick 2007; Harwood 1987). In his studies on the history of virology, Van Helvoort uses Ludwick Fleck's concepts of "thought-style" and "thought collective" to characterize these two perspectives, and in this project I will use the term "styles of reasoning" as defined by Hacking, and Fleck's "thought-styles" interchangeably because there are conceptually very close (and Hacking himself connects them explicitly in his 1992). The last issue of the journal *History of Science* is dedicated to the concept of *Ways of Knowing* and *Ways of Working* introduced by John Pickstone a decade ago. The contributors to this issue, however critical at times, make clear that the concept of styles or its cognates continue to have currency among historians and philosophers of science and medicine. But why continuing to talk about styles?

Firstly, styles are important analytic tools for historians and philosophers of science because they permit to study how concepts develop and grow within them, to use a biologic metaphor. Within styles, concepts can take on different and sometimes opposite, forms and meanings. As I want to argue, there was and continues to be, a (productive) tension between two broad styles of thinking about virulence, and this tension results from the intrinsic polarity of concepts expressed within styles. As historian of biology Jane

[10] For a critical review of Hacking's use of style see Kusch (2010).

Maienschein (1991) noted, there may be different schools or approaches within one style, which is, itself, embedded into distinct scientific traditions. Styles, also, are not necessarily delineated by national or disciplinary boundaries although they sometimes are. But in order to exist ontologically, styles do not have to be adopted by all scientists working on a similar problem, or at the same time.

In addition, styles are *epistemic* as they possess explanatory power to the extent that they frame what counts as evidence, relevant questions to ask, truth-value, and sound explanation in distinct research and/or cultural contexts (Maienschein 1991; for a contrasting view see Harwood 1989). In effect, alongside the development of distinct, individual styles of reasoning one finds the emergence of new standards for measurements, objectivity, proof, and so on (Hacking 1992). Although styles are flexible they are not loose or relativist categories; they admit rules, systems of norms, stabilization techniques, and methods of justification. As they become *stabilised* over time, entrenched within scientific activities, the very existence of styles of reasoning and their historical development become taken for granted. Styles, with time, become invisible.

Another important aspect of styles for historians and philosophers is that they illustrate how distinct scientific methods can be combined and survive signigicant changes in science. In other words, several styles can coexist in space at a given time. As historian and philosopher of biology Jean Gayon pointed out, the styles of reasoning outlined by Hacking and Crombie "did not succeed each other; they did not replace one another […]; some of them are extremely ancient, others are more recent, but they all have the remarkable property of having survived through time" (1999, 241). The persistence and dynamics of scientific styles over long periods of time characterizes the endogenous and exogenous styles introduced above. In effect, these methods of inquiry into the nature and causes of virulence have not superseded one another but alternated and developed in parallel in a relative isolation, although they sometimes overlapped, for instance with the construction of the category of emerging disease in the mid 1990s (chapter 6). Moreover, styles are appropriate to study science on long periods of time. As Hacking stressed, "styles of scientific thinking are not static. They persist in the *longue durée*, not because they remain immobile through centuries, like the Alps, but because they evolve,

because they react to new problems and criticisms, both internal and from outside" (Hacking 2005/2006, quoted in Kusch 2010, 164). Focussing on longer historical developments, in turn, allows for a broader view of concepts and their evolutions within distinct epistemic styles.

The French historian Fernand Braudel (1902-1985), one of the directors of the leading journal *Les Annales d'histoire économique et sociale* in the 1940s, introduced the concept of *long durée* history in *The Mediterranean and the Mediterranean world in the age of Philip II* (1949). In his book, Braudel argued that there are distinct temporalilties at work in history. In addition to the short-term history (or as we would say today, "micro-history"), one also finds intermediate and long-term historical trends. The merit of looking at history (of science) over periods of time longer than that of individuals or institutions is to make visible trends – or styles – that would otherwise remain unseen. One of the aims of the present project is to assess the wider significance of some scientific episodes (e.g. 1918 influenza pandemic) when placed in *longue durée* history perspective. The historian and biologist Michel Morange was the first to apply the concept of *longue durée* to the history of science (1994). Modulating the historical duration allowed him to question the philosophical significance of the so-called "molecular revolution" in biology in the 1960s. Some forty years before, Mirko Grmek, who supported Morange during his enterance into the field of the history and philosophy of biology and who was his "master" (Morange 2001), had applied the concept of *longue durée* to pathology and disease in his famous article on "pathocenosis" (1969), and later to the problem of the emergence of AIDS (1989) and other emerging diseases (1993; 1995). As Grmek was himself a pupil of Braudel there is a straightforward genealogy running from Braudel (history) through Grmek (history of medicine) and to Morange (history of biology).

Following this opened-path, a retour to *longue durée* history – without the grand narrative of the past – was recently advocated by a number of historians of biology (Rheinberger 2010b; Müller-Wille and Rheinberger 2007, 7) and medicine (Jackson 2011). Philosophers of science, however, are sometimes sketpcical to go down this road (Kusch 2010; 2011). One of the worries is that the concept of style becomes empty or thin once it is stretched over decades, or centuries. Another concern is to run the risk of losing sight

of the science as it happened in local contexts, by glossing over significant differences. My aim, however, is not to pitch "microstudies" against "big pictures" (de Chadarevian 2009) against each other. We will see that dividing up the history of science according to different temporalities, that is, moving between focussed cases-studies and longer views, can be done without falling back into the grand narrative of "total history" or leaving out important details.

Science is a highly diversified set of activities and consequently, there is a variety of scientific practices (Rouse 2002) including modelling, abstracting, representing, and so on. In this project I am mostly interested in scientific practices to the extent that they bear on the formation of concepts in the biomedical sciences. The formation and rectification of concepts is not (just) an intellectual task independent of scientific practices on the one hand; and conversely, concepts can be used as epistemic tools in various experimental and practical contexts, on the other. As Georges Canguilhem pointed out "it is at the level of questions, of methods" but especially, "of *concepts"*, that "scientific activity appears as such" (2005, 204 [1968]; emphasis mine). Analysing the coming into being of different styles allows for a deeper understanding of science as a practice (Rabinow 1994). Likewise, Maienschein also stressed, "science is not just thinking or just theorizing. It also involves doing" (1991, 410). Historians and sociologists of biomedicine Peter Keating and Alberto Cambrosio's concept of a "sytle of practice" (2007) is precisely intended to capture the *practical* dimension of the sciences. Indeed, the development of styles does not only involve mental but also material and practical operations. In this sense, talking about styles should help to capture a crucial part of what scientific activity is about: the aspect of "doing".

It may seem, however, that the terms "reasoning" and "thinking" are closely bound with writing and with the mind and they do not "sufficiently invoke the manipulative hand and the attentive eye", as Hacking put it (1992, 4). Hacking himself recognized that the expression "styles of reasoning" fails to fully capture the *practical* aspects of science, or science as a practice. But perphaps we should not separate too sharply the theoretical and the practical aspects of science, as both usually intimately coevolve. As Joseph Rouse emphasized, such would be misunderstanding the very concept of scientific practice itself (2002, 162). I suggest it is more accurate to describe theorizing and representing as being

different forms of scientific practices. Bruno Latour has long urged historians, philosophers and sociologists to look at "science in action" in order to grasp the different (social, economic, political) dynamics involved in the making of science and the construction of scientific facts (Latour 1987). Reworking Latour's suggestion, I want to argue that by looking at "concepts in action" one can achieve a clearer view on the relations between concepts and the set of scientific practices – or styles – within which they are embedded. In this sense, and despite Hacking's warning, I will talk about styles of reasoning (and thought-styles) *in practice*.

The coexistence of several scientific styles should call into question the idea of a unified picture of the sciences. While the goal of unifying different sciences through theory reduction has now largely been abandoned, philosophers have nevertheless found new ways of talking about unification, although by other means. In contrast with today's strong emphasis by philosophers on integration in science, however, my claim is that this divide between two distinct styles of practice is productive, leading to the development of new avenues, methods, questions, and objects of scientific research. Or, as Hacking put it, "styles […] open up new territory as they go" (Hacking 1992, 8). Inquiring into the formation of biomedical concepts provides a window into how disciplines, fields of research, and more generally scientific practices (such as concept formation) are shaped, and how the objects of study within these styles – the ontology –change and evolve over time. Moreover, identifying styles of reasoning and the concepts they harbour permits to establish links between separate fields that would otherwise remain largely invisible to historians, philosophers, and sociologists of science. Note, however, that I am not suggesting an evolutionary scenario in which one of these two approaches will eventually turn out to be the correct one, after competing with rivals. The claim is that it is in virtue of the *concept* of virulence itself, embedded within different styles of practices that we have a polarized understanding of the nature of virulence across the sciences nowadays. As the concept of virulence lends itself to different, sometimes incompatible meaning(s) this, in turn, facilitates and maintains this productive tension.

TOWARDS A MORE INCLUSIVE HISTORY AND PHILOSOPHY OF THE LIFE SCIENCES

Currently there is a strong disciplinary distinction between the philosophy of biology and the philosophy of medicine, on the one hand, and between these two and the history of science and medicine, on the other. One of the claims I wish to illustrate with the problem of virulence is that specialization in philosophy of science has gone far enough, perhaps even too far. It is becoming obvious that the analysis of a number of fields requires one to combine resources and skills from philosophy of medicine and biology. For instance, to understand and assess the claims of Darwinian medicine one needs to draw on both the concepts of health and disease in the philosophy of medicine and on the theory of evolution. Similarly, the concept of virulence is located at the crossroad of numerous scientific fields, and to study it one has to take many very different perspectives into account. In the end, to analyse the relations between evolutionary thinking and the health sciences in a way that is satisfying both from a philosophical and an historical point of view, one has to challenge the disciplinary boundaries set up by philosophers of biology and philosophers of medicine themselves in the past forty years.

Making connections between these groups requires us to be mutually aware of what their varying perspectives on medicine are, however. The approaches of philosophers of biology and of philosophers of medicine to the medical sciences remain somewhat independent and distinct. While philosophers of biology attend to the research side and attempt to study it in terms of their specific paradigm concepts of causation, mechanism and function, for instance, applying these as the framework for research on the human organism, philosophers of medicine are acutely aware that medicine is not strictly a biological science, but is situated in clinical practices. Interactions between the clinical side of medicine and research impact on the relevance, operation, and meaning of the concepts mentioned above. Disease is conceptualized in various distinct practices in the clinic, in labs, statistics and public health – and this multiplicity seems to resist unified causal models. The human organism, in turn, is perceived through a complicated prism of normal and pathological states, illness and therapy, fact and value, which determines how medical research selects what is of interest, what counts as explanatory for its goals, what is relevant for its practice and so on (Méthot et al. 2010, 294).

The present work draws on both Anglo-American and continental resources in the history and philosophy of science, and in particular on the work of Canguilhem, Rheinberger, and Hacking in historical epistemology. It attempts to make sense, both philosophically and historically, of the nature of the relationship between medicine and the health sciences, with a particular focus on the concept of virulence. Moving back and forth between field experiments, the laboratory, and the clinic, this project explores how the concept was shaped through two distinct, although sometimes overlapping, styles of practices, namely the exogenous and the endogenous styles.

THE EXOGENOUS AND THE ENDOGENOUS STYLES IN PRACTICE

The persistence of scientific styles is a feature that can be observed regarding the two styles of reasoning about virulence I outlined above. Like Hacking's styles of reasoning these two "methods" of inquiry into the nature and causes of virulence have alternated and even, sometimes, overlapped. In a chapter on his book *Les virus* published in 1891 "The evolution of ideas on nature and mechanism of virulence", French virologist Saturnin Arloing pointed out that virulence was for centuries characterized in terms of "fermentation" that is, as chemical reactions (Pasteur), but it was also, and at the same time, conceptualized as being the result of parasitism of one species by another (Raspail). According to the first model, virulence is a physicochemical reaction involving the action of enzymes in the organism, whilst on the other virulence is the outcome of a parasitic relation between a host and a pathogen. In the former, virulence originates from within, so to speak, whereas in the latter it results from an invading agent coming from the outside. These two approaches are surely very old, as Arloing observed, tracing their genealogies back into the Middle Ages.

Discussing the details of Arloing's argument further would require digressing for too long. My claim, here, is that the two ways of "reasoning" about virulence (i.e. "chemical" and "parasitic") as outlined by Arloing are still doing some important work today, although framed slightly differently. In effect, the two approaches Arloing outlined are roughly equivalent to functional and ecological explanations of virulence today, to the difference that both styles now draw on evolutionary biology. The distinctiveness of each

styles comes out particularly clearly when comparing how virulence is defined in medical bacteriology and molecular biology (e.g. virulence factors, pathogenicity islands, virulence genes, etc.) and how it is conceptualized by evolutionary ecologists (trade-offs between transmission, host immunity, and so on). We can trace the legacy of the divide between the exogenous and endogenous styles from the late nineteenth century and across most of the twentieth century, following two broad, parallel, and sometimes intersecting lines of research.

The exogenous style (chapter 4) was shaped at the turn of the twentieth century by the work of bacteriologist Theobald Smith in the United States. It grew into a full-blown "ecological vision" of infectious diseases (Anderson 2004) a few decades later with the work of Frank Macfarlane Burnet, Frank Fenner, René Dubos, and to some extent Joshua Leberberg. To explain why parasites harm their host, scientists within this style draw on the concept of "evolving parasitism" and on the "law of declining virulence", as defined by Smith. This law predicts that given enough time, any host and parasite relationship will evolve into a state of commensalism, where no harm is felt on either side. Disease thus indicates an incomplete or unsuccessful biological adaptation. Although it did not trigger a major discontinuity, the most important theoretical change in this tradition was the passage from the avirulence model to the mathematical and epidemiological model of the trade-off in the late 1970s. According to this other model there is a positive coupling between virulence and transmission such that virulence can either increase, decrease or become stabilized at an intermediate level over time. Evolution towards harmlessness, therefore, is not a necessary outcome of host and pathogens relations. Despite this change in understanding the evolution of virulence there is some continuity between the avirulence and the trade-off model as they both appeal to the concept of "balance" or "stable equilibrium" in a biological system that is established by natural selection. While the concepts of virulence genes and pathogenicity islands were quickly adopted by molecular geneticists they were, and continue to be, regarded with suspicion by evolutionary ecologists.

The second route through which virulence was studied runs parallel to the first in many respects (chapter 5). The endogenous approach, seeking determinants of virulence, grew mostly out of medical bacteriology, and particularly the work of Pasteur and Koch in

Europe. The French microbiologist Charles Nicolle was one of the first to suggest the possibility of a "material support" for virulence (1939, 66). It was, however, the English bacteriologist Frederick Griffith who pursued the virulence-based programme of Pasteur during the 1920s-1930s. Griffith's puzzling results in 1928 led, a decade later, Oswald Avery and his team to establish that the "transforming principle", as named by Griffith (who was able to return avirulent pneumoccocci to a virulent form, and vice-versa), was not a protein but DNA. From then on, the history of virulence became firmly intertwined with the history of heredity. A few years later, the discovery of plasmids (i.e. mobile genetic elements) by Joshua Lederberg (1952) opened up the door to the development of bacterial genetics, which facilitated a molecular understanding of virulence and pathogenicity. For instance, in the 1970s, microbiologist Stanley Falkow studied how plasmids and resistance factors can be hereditarily transmitted and can contribute to the pathogenicity of enteric organisms. His book *Infectious Multiple Drug Resistance* (1975) was one of the first contributions to the problem of antibiotic resistance from a molecular point of view. It is also Falkow who articulated "Koch's molecular postulates" and applied them to "microbial pathogenicity" (Falkow 1988). Working through the lens of the endogenous style, scientists progressively developed a number of powerful techniques to study virulence at the molecular, genetic, and more recently genomics, levels. One of the latest concepts within the functional approach of virulence is the concept of "pathogenicity islands", a region of virulence-associated genes in an organism's genome (Hacker et al. 1990; Hacker and Kaper 1999). It was hope that this concept would unambiguously demarcate virulent from avirulent organisms.

To summarize, this project aims at shedding new light on the relations between evolutionary thinking and medicine by looking at the natural histories of infectious diseases in the nineteenth and twentieth century especially. It also focuses on the ways in which evolutionary theory provides new insights into changes in the level of virulence and antibiotic resistance, in as much as they both contribute to the larger phenomenon of emerging diseases. Evolutionary processes can select for high virulence leading potentially to devastating pandemics, and for resistance genes among bacterial populations in hospital contexts, making common diseases more difficult to treat and facilitating the spread of nosocomial (hospital-acquired) diseases. These selective

processes are conducive of the upbringing of emerging infectious diseases on a global scale.

OVERVIEW OF THE CHAPTERS

Chapter 1 provides an analysis of a philosophical approach that is usually called "historical epistemology". Building on a new interpretation of Georges Canguilhem's history of concepts, I argue that taking concepts as units of analysis is compatible with a focus on scientific practices and experimental systems. In addition, this chapter explores the legacy of historical epistemology in the late twentieth century and sets the stage for the analysis of the concept of virulence in chapter 3, 4, and 5.

In Chapter 2, I analyse meaningful aspects of the historical and contemporary relations between evolutionary biology and medicine. After surveying some significant connections between Darwin's theory of evolution, eugenics, and medicine in the late nineenth and early twentieth century, I distinguish between Darwinian medicine and evolutionary medicine as follows: while the former attempts to understand health and disease in relation to human's distant biological past, the latter uses evolutionary theory as a complementary explanatory tool, enabling scientists to shed light on medical problems such as the spread of antibiotic resistance and the evolution of virulence in emerging infectious diseases.

Chapter 3 is more epistemological. It connects the idea that epistemically productive concepts are often those whose meaning remains "in flux" with a pragmatic approach of operationalism. It then examines the concept of virulence itself from the point of view of an operational analysis of concepts. Reviewing the definitions of virulence it is argued that an operational approach is well suited to explain the disunification and the state of "flux" of the concept across the life sciences. According to the perspective defended here, our understanding of virulence throughout most of the twentieth century was not the result of more fine-grained definitions but is rather the consequence of the concept being operationalized in distinct epistemic contexts.

Chapter 4 follows the elaboration of the "law of declining virulence and advancing parasitism" by Theobald Smith in the U.S. whose work on disease transmission provided the foundation for a new style of reasoning to account for the evolution and decline of infectious diseases: the exogenous or ecological style. After a close examination of the work of Smith, this chapter traces the legacy of this model across the field-lab border until its downfall during the late 1970s, concluding with its mathematical refutation by the epidemiological model of the trade-off. This chapter also links the avirulence hypothesis to the widely spread optimism that was then characteristic of modern medicine.

Chapter 5 analyses the conceptual developments of medical understanding of virulence in molecular biology, genetics and genomics from the perspective of an endogenous style of reasoning. Focussing on the material determinants of virulence, it shows how, within this tradition, virulence was intimately associated with problems of heredity and the structural basis of disease transmission. This other style of reasoning operationalized the concept of virulence in terms of the internal constituents of microorganisms, not in terms of their degree of adaptation to a particular environment.

Chapter 6 investigates how the two styles previously described started to come together following the introduction of the concept of emerging disease within public health discourses in the mid-1990s. However, an examination of the current molecular, ecological, and evolutionary explanations of the exceptional virulence that characterises the emerging 1918-19 influenza pandemic reveals the enduring polarization between the two epistemic styles. Whereas, ecologists and epidemiologists offer an account of the steep increase of virulence based on environmental factors, molecular pathologists investigate the whole genome of the influenza virus in order to locate the genes potentially responsible for its exceptional virulence. Both, however, draw on the theory of evolution.

Chapter 7, finally, explores some of the ethical issues related to the reconstruction of the 1918-19 influenza virus and other pathogenic organisms and how these call for a new and broader definition of the concept of emerging disease.

CHAPTER 1: FROM CONCEPTS TO EXPERIMENTAL SYSTEMS: TRENDS IN HISTORICAL EPISTEMOLOGY

INTRODUCTION

Notwithstanding programmatic statements there seems to be no emerging consensus among scholars as to whether the relation between philosophy and history of science is like a marriage of convenience (Giere 1973) or a more intimate kind of relationship (Burian 1977; see Schickore 2011).[11] As a consequence, the relations between both partners continue to be heated, debated, and even at times altogether contested (Hacking 1992, 1). The H and the P in "HPS" – standing for "history and philosophy of science" – remain in a state of "essential tension", to use Thomas Kuhn's expression (1977a), and convey the sense of a hybrid discipline (Chang 1999).[12] That philosophical analysis – especially when concerned with science but not only – has traditionally sought to attain general knowledge (or principles) whereas history's focus is on particular, and usually unique spatio-temporally located events, exacerbates the perceived rift between the aims and methods of history and philosophy of science further (Pinnick and Gale 2000). Based on citation analyses, a recent article even argued that there is no such thing as a field of history and philosophy of science *per se* and that HPS is at best a "sub-field of philosophy" itself (Wray 2010).

This diagnostic regarding the non-existence of a genuine field of HPS contains a kernel of truth but it applies only in very specific contexts either wholly dominated by a-historical analytic philosophy, or by wilfully inimical history scholars, allergic to philosophical reflection on the sciences – both entirely ignoring that any philosophical problem has a history and conversely, that the history of every branch of science has once relied, at one point or another, on philosophical conceptions and ideas. Wray's diagnostic is plainly estranged to a number of other intellectual traditions, in particular in France but also in Germany and elsewhere. In fact, there is a wide range of options available for who

[11] For instance, Lakatos' saying that the "history of science without philosophy is blind; philosophy of science without history of science is empty" (Lakatos 1970, 135).

[12] For Kuhn, however, the history and philosophy of science should remain separate domains (1977, 20).

wants to do HPS (and how) and such plurality in methods, styles, and approaches should be preserved and praised, not lamented on and rejected (Fagot-Largeault 2009).

The tension between generality and particularity just mentioned bears witness to the fact that philosophy and history have sometimes distinct (but not necessarily irreconcilable) epistemic goals. Even though, both the "historical" and the "practical" turns followed by many students of science in the late 1970s and early 1980s dramatically shifted the focus from finding general (even timeless) rules for knowledge production and discovery to the role of laboratory notes, material objects, scientific instruments and other apparatuses, themselves embedded at several levels of organization (national, international) within scientific research and practices (Brenner and Gayon 2009; Rheinberger 2000).[13] Those shifts brought out the tension between the *locality* of scientific knowledge (both historically and spatially), on the one hand, and the problem of the scope of its validity (i.e. knowledge is said to be universal), on the other. Scientific knowledge, supposedly valid everywhere, thus became seen as the result of *situated* (or local) practices and research programmes, generated in particular sites (e.g. laboratories), and not established *as knowledge* because in conformity with the natural world (Strasser 2006). As a result of those turns, the function(s) of experiments, for example, ceased to be regarded as mere hypotheses-testers for general, near-universal truth-claims. Experiments were reconceptualized as performative devices shaping scientific knowledge in various and rather unpredictable ways in local contexts (Hacking 1988, Rheinberger 1997). We could say that progressively, *doing* became seen as a legitimate way of *knowing*, as Hacking (1983) demonstrated.[14] The history of experimental practices opened-up new avenues to inquire into how experiments begin and end (Galison 1987),

[13] While the "historical turn" usually refers to the fact that philosophers of science began to use the history of science to thicken their analysis, the "practical turn" refers to a renewed emphasis on scientific practices, as opposed to theories or concepts. In both cases Hacking's *Representing and Intervening* (1983) and Shapin and Schaffer's *Leviathan and the Air Pump* (1985) are some of the earliest and most salient works that testify to these shifts. A visible sign of the shift from theory to practice in the history and philosophy of science is the new society for a Philosophy of Science in Practice.

[14] Knowking by doing is perhaps best exemplified by model organisms. Model organisms are both *models* (i.e. representations) of nature and *modelled* (i.e. shaped) according to specific research questions formulated by a scientific community (Ankeny and Leonelli 2011).

and more generally to examine what the specific status of different kinds of scientific *practices* within the whole of science, is (Rouse 2002).

The focus on a practice-oriented view of science prompted another – and perhaps until recently less perceptible– change in the historiography of science as well. Following the practical turn indicated above, the relevant time frame for historical analysis shifted accordingly, fostering rapid developments of micro (or local) histories of science intended to replace larger historical narratives that then prevailed (Rheinberger 2010b). Micro-histories focus on experiments, model organisms, instrumentations, and so on, and are usually contained within a short space and time framework. Along the lines of ethnography as initiated by Latour and Woolgar (1979), historians and social scientists began to closely examine a number of localized scientific practices (e.g. so-called "laboratory studies"), inquiring into the nature of "experimental systems" and "biomedical plateforms", rather than into scientific *concepts* as such, and their histories. Micro-history is the typical model of most history of science and medicine nowadays. As will be examined below, this shift in timescale underpins a larger one in terms of what the relevant unit of analysis in the history of science is.

A little more than a decade after this change of direction, philosophers and historians of science (re)discovered a *new* terrain to discuss the nature of the relations between the history and philosophy of science further with the help of a rather *old* label: "historical epistemology". From the mid-1990s onwards historical epistemology began to be frequently employed as a guiding concept by a small but growing number of historians and philosophers of science working at the then newly-opened Max Planck Institute for the History of Science in Berlin – headed by Hans-Jörg Rheinberger, Lorraine Daston and Jurgen Renn – as well as by philosophers of science whose names are usually more associated with Anglo-American philosophical traditions (e.g. Hacking 2002; 1992; Davidson 2001).[15] International conferences focussing on this topic brought together

[15] Hacking organized a week-long conference on historical epistemology in 1993. Nowadays, he prefers to use the label "historical meta-epistemology", a branch of a wider "historical ontology" (a concept he borrowed from Foucault) to characterize his own project (Hacking 2002). Although it would be going too far to claim that analytic philosophers in general are engaging with historical epistemology, see the special issue by Sturm and Feest in *Erkentnnis* (2011) where analytically-trained philosophers of science delve into the concept of historical epistemology.

scholars in the history and philosophy of science to debate the use (and misuse) of the concept of historical epistemology and its future applications.[16] During the last fifteen years the concept of historical epistemology not only (re)gained currency in philosophical and historical circles but suggested the possibility of bringing together the disconnected aims of history and philosophy into a more unified framework.[17] In this process of rethinking the relation between the history and the philosophy of science the emphasis placed on the experimental and practical side of science, as opposed to its conceptual dimension alone, also seems to indicate a marked difference between *newer* and *older* programmes in historical epistemology. The historian and philosopher of science Georges Canguilhem (1904-1995), whose views will be introduced and discussed below, is usually associated with an early tradition in historical epistemology, or "conceptual history" (Gayon 2009) where concepts unfold according to their own internal dynamic of change and rectification.

While it might appear that there is a natural convergence between Canguilhem's "concepts" and what Hans-Jörg Rheinberger – one of the latest heirs of historical epistemology – has called "epistemic things", the latter puts more emphasis on experimental system than on concepts, however. The most fundamental notion in Rheinberger's epistemology, indeed, is not concepts but "experimental systems" within which "epistemic things" and "technical objects" interact in an unpredictable way, generating novelties and "allowing cognitive spatiotemporal singularities to emerge" (Rheinberger 2000, 285; 1997). Experimental systems are precisely, in Rheinberger's words, "the smallest integral working units of research" (1997, 28). In fact, Rheinberger's interest lies in the development of an epistemology of *experimentation* within a larger

[16] In addition to Hacking's conference in Toronto in 1993, one of the largest conferences on historical epistemology was organized at the MPI in July 2008 by Thomas Sturm and Uljana Feest. Later the same year, a second conference was organized at Columbia University. In December 2009, the University of Leuven in Belgium also held a conference on historical epistemology. Another conference on the theme of historical epistemology, and more precisely titled From Bachelard and Canguilhem to Today's History of Science, was organized in December 2010 and was also hosted by the MPI.

[17] Importantly, the way the term "epistemology" is employed by most of these thinkers (and here) does not correspond to the philosophical discipline understood as a branch of philosophy concerned with the study of knowledge and justified beliefs. In contrast, the term "epistemology" here refers to the ways in which knowledge production is historically possible and changes over time and on the relations between abstract scientific concepts and concrete material equipment in which these concepts emerge (see Rheinberger 2010a, 2).

practice-oriented history and philosophy of science. Looking at "the power of material objects" driving scientific research, not only in relation to *concepts* (or what Canguilhem called "scientific objects") or *ideas*, but in relation to the entire and larger experimental systems in which those objects or concepts are embedded and shaped (Rheinberger 2005; 1997), this new approach stands uneasily with the previous perspective of historical epistemology. The tension I am trying to capture and render here stems, on the one hand, from the choice of a different *unit of analysis* for the history of science (i.e. concepts versus systems), and from the way in which this choice itself leads to adopting a wholly different epistemological approach to science and scientific change (concept-based versus practice-based), on the other.

Drawing on scholars from various philosophic horizons, including Bruno Latour, Michel Serres, Jacques Lacan, and Jacques Derrida, Rheinberger's work has been (and continues to be) strongly influential beyond the borders of the history and philosophy of science, having set a firm foot-hold in several other disciplines, including anthropology, the social studies of science, and literary studies (Lenoir 2010). Whereas Rheinberger quickly rallied a great number of academics to his practice-oriented view of science, Canguilhem's views on the history of science, however, were increasingly charged with inadequacies from historians, sociologists and philosophers of science.[18] This situation is puzzling for at least two reasons: firstly, on many occasions, Rheinberger draws extensively on the work of Canguilhem, in particular his work on concepts. [19] This suggests that by going below the surface resemblances one can identify some underlying common ground, or a shared motivation, between the two, as well as between older and newer programmes in historical epistemology; and secondly, while his epistemological approach to the history of the life sciences was strongly criticized and eventually rejected (e.g. Hodge 2000), Canguilhem's earlier analyses of the concept of the normal and the

[18] Hodge (2000); Zibakalam (1996); Bowker and Latour (1987).

[19] Rheinberger has often analysed Canguilhem's tripartite distinction between natural, scientific and historical objects (2010b; 2005c). His observations on Canguilhem's concepts somewhat echoes his own notion of "epistemic things" which he defines as things that "present themselves in an "irreducible vagueness", embodying what "one does not yet know" (1997, 28). For instance, Canguilhem once suggested that the object of the historian of science and the object of the sciences are not the same as the former are doubly individuated, being situated at another level of abstraction. The history of science then "practices on these second, nonntatural, cultural objects" to which "*incompleteness* is essential" (Canguilhem 2005, 203 [1968]; emphasis added).

pathological (1943) are now gaining momentum,[20] winning him some years ago the (paradoxical) title of a "vital rationalist" (Rabinow 1994).[21] This second point is all the more surprising as *The Normal and the Pathological* not only supports Canguilhem's later analyses on the intricate relations between scientific practice, techniques, and concepts but also sharply examines a category central for the present chapter and for recent work in the history of science, that of "experimental". How do these trends in historical epistemology relate to one another? Can they be reconciled? I hope to show that the answer to the last question is definitely affirmative.

This puzzle and those interrogations spearhead the development of this chapter where I want to argue more precisely that (a) Canguilhem's philosophy of the concept needs to be re-evaluated and that it is in fact much richer and more relevant to current philosophical debates than is commonly assumed, and (b) that in particular Canguilhem and Rheinberger's approaches are quite compatible, even though they choose different units of analysis. Based on text analyses, I show that the nature of concepts in Canguilhem's work has been misunderstood, and in particular that the role of practice, techniques and experimentation in concept formation was largely overlooked. My defense of Canguilhem's (historical) epistemology will illustrate how both the criticisms voiced against his conceptual approach and the perceptible distance separating his work from recent studies in historical epistemology dissolve, once we move beyond Canguilhem's image – an image he somehow himself contributed to promote – as concerned with disembodied, abstract genealogies of concepts. Drawing especially on *The Normal and the Pathological* (1943) and on *The Formation of the Concept of Reflex* (1955), I will show that the formation and transformation of a concept, in Canguilhem's sense, is intrinsically connected with the experimental, material, technical, and cultural contexts in which a concept is operationalized. The new reading of Canguilhem's philosophical legacy shows there is no sharp discontinuity between "old" and "new" historical epistemology perspectives, and further suggests that Canguilhem anticipated a

[20] For a commentary and a reassessment of *The Normal and the Pathological* see Keating (2001). For a discussion of Canguilhem's medical thesis in contemporary philosophy of medicine see Méthot (2009a, 42-46).

[21] This expression is indeed paradoxical because vitalistic biologists are often considered to be anti-rationalists (Canguilhem 2008 [1952]).

number of claims (e.g. links between concepts and scientific practices) that are now in the process of becoming the norm among historians and philosophers of science.

Beginning with a short history of French historical epistemology, the next section introduces some of Canguilhem's most important critics in the past fifteen years. In order to show why those arguments fail to convince, I then examine three different units of analysis in the history of science and those analyses are further supported by an examination of Canguilhem's early views on technique (even phenomeno-technique), science and life, and the idea that concepts take on new meaning following not only theoretical contexts in which they are embedded, but distinct operationalizations. Finally, the last section of the chapter covers the normative aspect of Canguilhem's concepts and discusses how, despite a deep respect for science and scientific practices, the authority of which he did not seek to undermine, Canguilhem's conception of the object of the history of science can help philosophers and historians to free themselves from the tutelage of science.

A SHORT HISTORY OF (FRENCH) HISTORICAL EPISTEMOLOGY

Even if the renewed interest in historical epistemology is closely linked to the work of a number of scholars at the Max Planck Institute its beginnings are located elsewhere. The original (French) context of emergence of the concept and tradition of historical epistemology are often left partially – sometimes even completely – untold by those who appropriated the label for their own project, however (Gingras 2010). [22] Throughout the twentieth century historical epistemology (or conceptual history) became especially associated with the work of Gaston Bachelard, Georges Canguilhem, and Michel Foucault (Brenner and Gayon 2009, 8; Braunstein 2008). While Bachelard (so far as I know) never used himself the expression "historical epistemology", Dominique Lecourt, a former student of Canguilhem, was certainly the first to write a book on Gaston Bachelard's *épistémologie historique* (historical epistemology) in 1969. This book, shortly followed by

[22] Although historical epistemology is often characterized as "French epistemology", it was also developed by philosophers working *outside* France (Schmidgen, 2008; Bontens, 2005). Other scholars like Arnold Davidson have used the concept of historical epistemology in the French context (particularly following Foucault). See also Rheinberger (2005; 2010a; 2010b).

Marxism and philosophy: Bachelard, Canguilhem, Foucault (Lecourt 1975), propelled the concept of historical epistemology on the philosophical scene, next to Kuhn's "paradigm" and Lakatos' "research programme" in the mid-1970s.[23] Since then, the expression historical epistemology has come to designate Bachelard's way of practicing epistemology as well as the work of many of his students and followers, including Canguilhem and Foucault, but also Camille Limoges, Francois Dagognet, Dominique Lecourt, Susanne Bachelard, Claire Salomon-Bayet, Francois Delaporte, Michel Serres, Christiane Sinding, and many others.

Amidst the recent debates and controversy regarding the origin and history of historical epistemology, Dominique Lecourt admitted he borrowed the concept from Georges Canguilhem himself (Lecourt 2008). Curiously, though, Canguilhem did not use the category "historical epistemology" programmatically, methodologically or otherwise. In fact, he may have used it only once or twice, in a slightly critical way, and not to characterize the philosophy of Bachelard or his own (as we often do today), but to indicate what he considered to be an overtly descriptive and linear way of engaging with the history of a science (2002, 178). In contrast, he credited Bachelard for doing "historical history" by which he meant the ways in which Bachelard was attentive to the role of errors and "rectification" in science. For some readers, these comments may chime in with Canguilhem's idea that the history of a science should not to be written as an "unfolding" – i.e. as a linear and preformed development – but instead as an "adventure" – i.e. as an open-ended process (1977, 157). Yet, by claiming that "in some sense, epistemology has always been historical" (1988, 10), and in the light of numerous historical essays, Canguilhem aligned himself fully with the tradition and the significance of a genuine *historical* epistemology.[24] Indeed, except on rare (and mostly commemorative) occasions Canguilhem's philosophy of science (or epistemology) is developed alongside meticulous analyses of well-chosen episodes in the history of science, not apart as meta-discourses on science. For Canguilhem, such disconnected

[23] For an analysis of the Marxist roots of historical epistemology see Gingras (2010, 442-443).

[24] See the collection of Canguilhem's essays recently translated as *Knowledge of Life* (2008 [1952]).

discourses, in fact, would themselves be tantamount to the (positivist) idea of a "scientific method" (Balibar 1993, 61).

Given Canguilhem's critical stance towards the concept, if not the content, of historical epistemology, we can understand better his frank response when Lecourt asked for his approval to use the expression for his book on Bachelard. In an often-told anecdote Canguilhem is said to have replied to Lecourt "No! Not historical epistemology but epistemological history" (Lecourt 2008; Gayon 2003). Lecourt, however, did not follow Canguilhem's recommendation although he remained careful to speak of Canguilhem's "epistemological history" (Lecourt 1975). Some have detected in Lecourt's philosophical choice a corroboration of their intuition that Bachelard and Canguilhem's methods differ significantly (Rheinberger 2005; Gayon 2003; Gutting 2001).[25] Recently, historian and sociologist of science Yves Gingras radicalised the difference between the two approaches arguing that "if we use the language correctly, 'historical epistemology' is kind of epistemology and not a kind of history and 'epistemological history' is a kind of history and not a kind of epistemology" (2010, 444). Gingras argues that *historical* epistemology places more emphasis on the *philosophical* than on the *historical* aspects of this project (and so better characterizes thinkers like Bachelard and Hacking who used history for philosophical purposes); whereas *epistemological* history is more adequate for historically-oriented authors. Both Gingras and Lecourt agree that "epistemological history" is overall a better label for Canguilhem's project which is (they gather), of a more historical nature.[26] But Canguilhem himself, at times, felt the history of science had to be "underpinned" by a philosophy of science which, in turn, must be supported by a "theory of knowledge" (1949). Here, I will not attempt to deepen what the differences between historical epistemology and epistemological history may be, although I will characterize the work of Canguilhem as one of the best examples of historical epistemology in a wholly

[25] In retrospect, Rheinberger sides with this interpretation as indicated by the change to the title of his article on Canguilhem (2005) from "Reassessing the historical epistemology of Georges Canguilhem" to "Epistemological history" when it was recently republished (2010b).

[26] Gary Gutting also distinguished Bachelard and Canguilhem as the former being more a philosopher and the latter a historian, although he recognized at the same time that Canguilhem's historical work "cannot be sharply separated from his generally Bachelardian philosophical viewpoint" (2005, 10; 1990, 137).

philosophical sense.[27] While Gingras' definition is accurate (i.e. that historical epistemology does encompass philosophically-oriented histories of science) it is, however, missing the point than to try to pigeon-hole thinkers as being either on the philosophical or on the historical side of the fence. Moreover, the the real interest of the concept of historical epistemology is precisely that it *indistinctly links the history and philosophy of science together in a single, coherent project*.

A short time ago, philosophers of science Uljana Feest and Thomas Sturm attempted a typology of historical epistemology which, according to them, is often understood as 1) a study of higher epistemic concept (e.g. objectivity, observation, probability); 2) the study of historical trajectories of particular scientific objects of research (e.g. electron, phlogiston, DNA); and 3) as the long term study of scientific developments (2011). According to them this typology remains open and does not intend to be exhaustive. Indeed, those categories can apply by degrees as we can easily envisage a project that encompasses all of them or that, conversely, neglects most of them. However, these categories apply only partially to historical epistemology as practiced by Canguilhem.

Indeed, we can underline three aspects of historical epistemology as usually understood in France. Firstly, the history of science in France has always been a philosophical project; there is no sharp distinction made between the history and philosophy of science. The idea of a *historical* epistemology has itself a long history and goes back (at least) to Auguste Comte's saying that "we do not know completely a science if we do not know its history" (Comte 1869, 65, quoted in Gingras 2010, 447).[28] Dominique Lecourt summarized the situation well enough when he said that "the discipline which takes scientific knowledge as its object must take into account the historicity of that object" (1973, 25). In this sense, the concept of historical epistemology is interesting because it can help us to move past the debate between the history and

[27] This is also one of the most common denominations for Canguilhem's approach. See Chimisso (2003); Rose (1998).

[28] In a recent communication in Berlin Jean-Francois Braunstein (2010) pointed out that the expression can be found in the work of Abel Rey, founder of the Institut d'histoire et de philosophie des sciences in 1938 where Bachelard and Canguilhem have succeeded one another as its directors.

philosophy of science in the anglo-american world that is still going on (see Schickore 2011).

Secondly, epistemology (or philosophy of science) is necessarily interwoven with historical analyses because without this historical dimension, "epistemology would be a completely superfluous duplication of the science about which it pretends to have something to say" (Canguilhem 1968, quoted in Rheinberger 2010a, 66). History, here, provides the critical distance necessary to philosophically evaluate scientific claims in the light of new and recent findings. Rejecting the old-fashioned idea of a timeless scientific method, Canguilhem endeavoured to analyze the developments of the life sciences from an historical standpoint in order to avoid redundancy with science itself. It is notworthy that "epistemology", understood as a theory of knowledge, is usually absent from the French discourses on the history and philosophy of science. Epistemology, in contrasts, is understood as the operation of restituting, a posteriori, conceptual and practical forms of knowledge in a given domain.[29]

Thirdly, there is a normative element in the historic-philosophical method developed by Bachelard and by Canguilhem. Historians and philosophers must not only observe and select the "facts" but they must also "judge" them as being part (or not) of the science of today. With the metaphor of the "tribunal" Canguilhem tried to convey this normative stance which stood in sharp contrast with predominant views according to which the history of science is not just the "memory of science" but is also its "epistemological laboratory".[30] Canguilhem gave the example of 18th century botanists which, for "pure historians", would be "nothing but what botanists of the period would take to be within their scope of inquiry [...] But does this science of the past constitute a past for the science of today?" (1988, 3) For Canguilhem, the past of a science is not given but must

[29] "For the epistemologist, practicing a science amounts to mimicking the practice of the scientist by attempting to reconstitute the means by which knowledge is produced through studious attention to the papers in which the producer explains his behavior" (Canguilhem 1988, 8). As a footnote in Canguilhem's text indicates, with a reference to the work of Grmek on Claude Bernard, this definition of the practice of epistemology is broad enough to include not only published articles but also laboratory notes and notebooks "in which a scientist attempts a posteriori to rationalize his experimental methods" (1988, 20).

[30] This metaphor that the history of science is the laboratory of epistemology is usually attributed to Edward J. Dijksterhuis.

be reconstructed and therefore cannot be equated with the science in the past. Cast in the light of epistemological analysis, the history of science becomes a genuine philosophical endeavour, not designed only to validate (or reject) philosophical claims but primarily to allow for a better understanding of the diversity of scientific practices, as seen through the emergence of methods, objects, styles, and concepts.[31] This is how the expression historical epistemology will be used and understood in the following pages. The next section will analyse two important criticisms voiced against Canguilhem's historical epistemology.

CRITICS AND CRITICISMS OF G. CANGUILHEM'S CONCEPTUAL HISTORY

Recent translations have given Canguilhem's ideas on biological individuality, normality, and the concepts of health and disease new vigor and relevance to evaluate and criticize, from a fresh perspective, various claims in contemporary biomedical sciences.[32] Yet, in the last two or three decades a number of criticisms were voiced against his conceptual history (Bowker and Latour 1987; Hodge 2000), and epistemology especially as developed in Canguilhem's *Ideology and Rationality in the Life Sciences* (Zibakalam 1996). I will mostly concentrate on the first two here, reserving a fuller analysis for the third one on another occasion.

One of the strongest disagreements with French historical epistemology was made, ironically, from another Frenchmen: Bruno Latour. Together with Geof Bowker, he compared the diverse trends of social studies of science and history of science in French and in Anglo-American contexts (1987), remarking that Canguilhem and Bachelard are "the two giants of French social studies of science". Bowker and Latour, however, went on to suggest that "French workers in the field could see much further *without* those two giants standing on their shoulders" (1987, 741; emphasis added). What was particularly at stake in the sociological reception of Bachelard and Canguilhem in France in the 1970s and 1980s was the marked distinction they advanced between pre-scientific and scientific

[31] "To do the history of sciences [...] is one of the functions, and by no means the easiest, of philosophical epistemology" (Canguilhem 2005, 206 [1968]).

[32] See Canguilhem's *Knowledge of Life* (2008 [1952]).

spirit (Bachelard) or, between science and ideologies (Canguilhem) which many saw as going against the "principle of symmetry" introduced by the advocates of the "Strong Programme" (i.e. Barnes and Bloor) in the sociology of scientific knowledge (Tiles 2009). This line of criticism was driven by a sense that in France, science was often depicted "as something somehow apart from society and history", a situation with deep political and social consequences, according to Bowker and Latour (1987, 717).[33] However, for others, Canguilhem's "scrupulous respect for the reality of real science", as Althusser put it, is what permitted the emergence of a new kind of epistemologists who, "similar to ethnologists", "go into the field", to overturn the problems of classical epistemology (1998, 163 [1964]). Strikingly, Althusser compared Canguilhem to ethnologists studying scientists in their own milieu, an idea frequently associated with Latour's own laboratory studies and the several ones he fostered.

For the purpose of this article, another (and more recent) line of criticism, one that comes directly from the history of science itself, is particularly relevant as it directly calls into question the adequacy of "concepts" as units of analysis and narration for the history of science. In an article published as part of a collective journal issue dedicated to the work of Georges Canguilhem, historian of biology Jonathan Hodge attempted to unravel the roots of Canguilhem's own historical approach to the life sciences. According to Hodge's analyses, Canguilhem is more "English" than we usually suspect and his thinking perhaps needs "liberating" with the help of German philosophers. The seemingly paradoxical situation Hodge describes amusingly is that despite sharp criticism, Canguilhem has always admired the work of the positivist Auguste Comte.[34] In turn, Comte was profoundly influenced by Condorcet who himself owed a great deal to the philosophy of Bacon and Newton. This genealogical method as applied to Canguilhem's personal trajectory makes him look more English than French! Hodge complains, however, that more importantly Canguilhem's "preoccupation with concepts" has

[33] Latour, however, did not wholly dismiss Bachelard's philosophical examinations of science. He thought, however, that those comments would "make better sense when set within a sociological framework" (Latour and Woolgar 1979, 258). An example of a sociological analysis of Bachelard can be found in Gingras (2003). For a defence of Canguilhem's work from a science studies point of view, see Nicholson (1991); Rose (1998); Tiles (2011).

[34] For an analysis of the influence of Comte on Canguilhem see (Braunstein 1998).

seriously confined his agenda as an historian of science by neglecting both the role by played interests and institutions and the influences of predecessors and scientists' intentions on scientific progress (2000, 72).

Hodge is convinced that Canguilhem's method is wholly inadequate to its object of study, and he goes on to claim that, for example, "any historical analysis of the *Principles of Geology* cannot succeed if it restricts itself to an analysis of concepts" (2000, 72). According to Hodge:

> A historiography for science that concentrates our attention on *concepts* cannot do justice to the challenges we face as historians. Nor, *in any case, is the concept a very suitable unit of analysis and narration.* For a concept is a product, an achievement not a process or a goal. The concept, then, *as a unit of analysis* and narration is *not adapted to the historian's quest* of insight into the process of enquiry that Lyell or Darwin, or Bernard or Monod, have undertaken, or for insights into the aims that inspired and directed those activities (2000, 72-73; emphasis added).

To rephrase Hodge's argument, conceptual history should be rejected because it neglects the role of influences and institutions, on the one hand, and concepts are the wrong units of analysis to understand science historically and dynamically, on the other, because firstly, they are static entities, whereas science is presumably characterized by dynamic and change; and secondly, because the aims of scientists are irreducible to the formation of concepts. Thus, when Charles Lyell wrote the *Principles* or when Charles Darwin opened up his *Notebooks* they both had a number of goals in mind such as reforming the science of geology, or introducing new methods of classification, none of which are reducible "to an intention to construct one or more concepts" (Hodge 2000, 72). In brief, Hodge accuses Canguilhem of providing a wholly internal history of science, one that leaves out the role of social institutions, intentions and beliefs. Echoing Latour's concerns, Hodge also points out that Canguilhem's focus on concepts has constrained the scope of his historical analysis by neglecting the social and political influences on the

development of the sciences.[35] As a consequence of these shortcomings, Hodge argues, Canguilhem's methodology fails to provide historians with "insight" into the process of scientific enquiry. While this line of critique raises important issues it is, however, based on an oversimplified view of what Canguilhem's concepts are. As the next sections will illustrate, a "preoccupation with concepts" can lead not only to a "broad intellectual view of science", as Hodge points out (2000, 71), but also to a more embodied view of concepts and scientific practices.

UNITS OF ANALYSIS IN HISTORICAL EPISTEMOLOGY : A (TENTATIVE) TAXONOMY

Historians and philosophers of science can historicize a wide range of "objects" and "processes", including concepts, theories, ideas, models, experimental systems, institutions, and so on. Within the tradition of historical epistemology discussed here, however, concepts and experimental systems occupy a privilegied place and this section will focus on these units of analysis in particular. Before turning to them, I first discuss the notion of "ideas" as units of analysis in the history of science to mark the transition to "concepts" and later "experimental systems".

IDEAS

Historians of science have long been interested in the nature and roles of concepts, although these were not always the main analytic notion to understand and interpret science. Prior to concepts and experimental systems, Alexandre Koyré (1892-1964), one of the most important historians of science during the first half of the twentieth century, strongly emphasized "scientific ideas" as the relevant unit from which to reconstruct and understand the history of a science, for instance astronomy. *From the Closed World to the Infinite Universe* (Koyré 1957) championed the view that theories and ideas reflect the true essence of science, and even govern its process. Because of his intellectualist

[35] This critique persists in new forms of historical epistemology. In a recent paper, philosopher Martin Kuch raises three objections to new work in historical epistemology such as Hacking's, and Loraine and Galison's work on objectivity. For a reason similar to Hodge's critique of Canguilhem, Kusch argues that those recent works fail to meet what he calls the "microhistory point", namely to analyse intentions, institutions, and interests in the development of scientific knowledge (Kusch 2011).

approach Koyré was often accused of providing a strictly "internalist" account of the history of science. Recent scholarship has shown Koyré's work to be, however, more nuanced (Stump 2001; Elkana 1987). Nevertheless, his *Galilean Studies* published in 1939 strongly challenged those who, like the Soviet physicist Borris Hessen (1893-1938), attempted to explain the emergence of modern science by appealing to social factors alone.[36] In the historiography of science Koyrés is primarily remembered as the one who asserted the primacy of *theoria* over *praxis* in driving science forward. Indeed, Koyré's approach oriented to metaphysical world views mostly emphasized the development of theories and downplayed the role of experiments. It could be said that Koyré's idealistic (or Platonic) approach was "to a certain degree even antiexperimental" (Rheinberger 2010, 52). Many other historians of science shared a number of Koyré's epistemological positions such as the rejection of the concept of "precursors" in the history of science; the role of errors and truth in the transformation and rectification of scientific knowledge; the discontinuous aspect of scientific revolutions, and the importance to situate scientific problems against their own cultural, metaphysical, philosophical, and historical backgrounds.

Canguilhem and Koyré knew each other. They met for the first time at the "Congrès Descartes" in 1937 – an international conference in philosophy held in Paris. On this occasion Canguilhem gave his first philosophical paper on "Descartes et la techniques", to which I will come back later. This encounter with Koyré left a lasting mark on the young philosopher, not yet physician or historian of science (Canguilhem 1987).[37] In his work prior to his becoming known as an historian of science, Canguilhem's most important reference in the history of science was Koyré, not Bachelard. For example, in an essay on "Le rôle de l'histoire des sciences dans la philosophie des sciences : l'établissement des faits fondamentaux de la dynamique" (1949) written six years before he became head of the Insitut d'histoire des sciences, Canguilhem draws heavily on Koyré's analyses while the name of Gaston Bachelard is mentioned only once. With time, however, Koyré's name

[36] Hessen gave a famous paper at the Second International Congress of the History of Science, held in London in 1931, titled "The socio-economic roots of Newton's *Principia*". This paper motivated the development of an externalist approach in the history of science that was later challenged by Koyré.

[37] A detailed and systematic comparative analysis of Canguilhem's and Koyré's *oeuvres* has not yet been attempted and is beyond the scope of this chapter.

faded out slowly from Canguilhem's writings while Bachelard's gained prominence, a shift that runs parallel with the moment Canguilhem succeeded Bachelard as the head of the Institut d'histoire des sciences in 1955.

Although the name of Koyré continued to appear in Canguilhem's writings after this date,[38] and even in relation to Bachelard's epistemology to whom his work relates, Canguilhem was moving towards a new kind of history of science, one where the "typical units of knowledge" are not theories, ideas, or phenomena anymore but "concepts" (Balibar 1993, 68; see Gutting, 1990, 137). Yet what is the difference between concepts and ideas, and what difference does it make in terms of historiography? Regarding the first question, one of the differences between concepts and ideas, as it will become clear later, is that a conceptual history, in Canguilhem's sense and in contrast with Koyré's approach, advocates a much closer focus on scientific practice, instruments, and techniques than the latter. As to the second question, it follows from the emphasis on concepts, once correctly understood, that a history of conceptual changes will place equal emphasis on the development of scientific *practices* in which those concepts are operationalized and embedded.

CONCEPTS

In a tribute article to Georges Canguilhem, Michel Foucault credited his mentor for promoting a "philosophy of the concept", as opposed to a "philosophy of the subject", placing at the same time *épistémologues* (Bachelard, Cavaillès) and *phénoménologues* (Sartre, Merleau-Ponty) in two distinct and rarely overlapping philosophical traditions, at least in France (1991 [1985]). There is little doubt, in fact, that whichever name we give to Canguilhem's philosophy, the central notion in it is that of a *concept*, not theories or ideas. As Lecourt pointed out, "Canguilhem concerns himself more with the descent of concepts than with the concatenation of theories" (1973, 171). Following Foucault, commentators noted that Canguilhem's approach consists in applying the "principle of the genealogy of concepts" (Macherey 2009, 113-114; Badiou 2009, 7). In fact, this aspect was first noticed by philosopher Pierre Macherey in an article published more than

[38] For instance, in the essay on "The Object of the History of Science" (2005 [1968]).

twenty years before Foucault's tribute mentioned above, in a Marxist journal. In this first systematic study of Canguilhem's philosophy of science Macherey wrote that "Canguilhem substitutes *the filiation of concepts to the chain of theories*" (1998, 171 [1964]; italics in original). A historic-philosophical approach *à la* Canguilhem consists thus primarily in following concepts over time and across scientific disciplines (and ideologies) in order to locate significant shifts (i.e. "rectification") regarding meaning and domains of application. According to Gilles Renard (1996), unravelling the trajectory of concepts was Canguilhem's objective. Likewise, Fichant and Pêcheux's *Sur l'histoire des sciences* stressed that in contrast with the "intellectual history" inherited from Koyré, Canguilhem sought to develop an approach to the history of science based on the filiations of concepts (Fichant and Pêcheux 1969).

Of course, Canguilhem was not alone in promoting similar conceptual approach to science in France at the time but as Yves Schwartz pointed out, if compared with other "philosophers of the concept" he appeared to them "as a singular character in the conceptomania – which was largely indebted to him – during the 1950s-1960s" (1993, 307). It is unsurprising that commentators attentive to the work of Canguilhem, in addition to his students, have been listening to "the discipline of the concept" (Schwartz 1993, 305). This received-view of Canguilhem's epistemological method, formed between the 1960s and the 1990s, remains the dominant interpretation today, although philosophers rarely explain what a concept, for Canguilhem, is. Concepts occupy a central place in science and because of this, Canguilhem claims, they deserve much philosophical and historical attention.[39] A few years after he became head of the Institut d'histoire des sciences in Paris, Canguilhem suggested that "the history of science" cannot be satisfied with collecting biographies of scientists but […] "has also to be a history of the formation, deformation, and rectification of scientific concepts" (2002, 235 [1963]). As his detailed historical analyses reveal, Canguilhem had a broad vision of what the history of science

[39] Canguilhem wrote that "to be ironical with regard to the importance given to concepts is easier than to try understanding why without them there is no science" (2005, 204).

should be like, one that reaches beyond the determination of epistemological breaks or conceptual filiations, however.[40]

Both the centrality and the lack of clarity of the notion of a "concept" in Canguilhem's writings need to be (re)evaluated and examined more closely. Even Canguilhem's perception of his method can be misguiding, and if we rely on his own account alone, paraphrasing Yehuda Elkana's assessment of Alexandre Koyré, we will not be able to break out of the confines of the usual images of Canguilhem as a philosophical historian of disembodied concepts (1987, 136). The experimental or practical dimension of Canguilhem's epistemology is original even though it is often left out by commentators who focus largely (if not exclusively) on the notions of "filiation" and "genealogy" of concepts. And yet, Canguilhem's conceptual history was from the very beginning, practice-oriented, as his first articles on the relations between science and techniques illustrate. In a word, what Canguilhem promoted is an epistemology of *conceptual practices*. The interpretation of Canguilhem I propose in this chapter could, moreover, provide a way out to reconcile what often appears as a rupture in French philosophy, history, and sociology of science in the 1960s and 1970s, disconnecting the (applied) rationalism of Bachelard and Canguilhem from the work of Foucault, Deleuze, Derrida, Bourdieu and many others. By focusing on Canguilhem's notion "practice" and Bachelard's "phenomeno-technique" we can understand better the emergence of contributions such as *The Logic of Practice* of Bourdieu in the 1980s, for instance.

EXPERIMENTAL SYSTEMS

The historian and philosopher of science Hans-Jörg Rheinberger is one of the latest descendents of this tradition in (French) historical epistemology. Trained in continental philosophy, Rheinberger translated and introduced the work of Derrida and Lacan to German-speaking audiences in the 1970s. For more than ten years he also worked at the Max Planck Institute for Molecular Genetics in Berlin while at the same time pursuing his

[40] Indeed he gladly admitted that the history of science "distinguishes and admits many levels of objects of analysis in the theoretical domains that it constructs: documents to catalogue; instruments and technique to describe; methods and questions to interpret in addition to concepts to analyse and criticize" (Canguilhem 2005).

investigations of the roots of historical epistemology which he locates in the work of Ludwig Fleck, Edmund Husserl, Gaston Bachelard, and Georges Canguilhem (Rheinberger 2010a). While a director of the Max Planck Institute for the History of Science, Rheinberger emerged in the late 1990s as a prominent figure in the history and philosophy of science, armed with a promising set of "categories of discourses" – including epistemic thing, experimental system, and experimental cultures – most of which are foreign to Anglo-American philosophers of science, as Richard Burian (1995) observed. Although Rheinberger does not often directly engage Anglo-American philosophers in his written work he neverhtless is closely related to the rise of philosophy of biology as an academic discipline, and in particular with Marjorie Grene. In a review of Rheinberger (1997), Grene wrote that the latter is guiding philosophers of science in "the direction they need to go to escape the sterility of philosophy of science in its once 'received' forms, or of the 'social constructivist' mode that has sometimes replaced it" (2002, 574). Two years before that, Grene had written a lengthy paper on Canguilhem's philosophy of science in which she noted a convergence between his and Rheinberger's attempt of staying close to scientific practices (Grene 2000).[41]

Canguilhem and Rheinberger have met only once (Rheinberger, personal communication), but Rheinberger entertained a long lasting interest in the spirit of French historical epistemology. His work, indeed, is especially informed by, and characteristic of, the style of Bachelard and Canguilhem where the links between philosophical reflection and historical analysis are tightly interwoven, even indivisible. Inheriting the richness of a long tradition in the history and philosophy of science, Rheinberger reinterprets and reactivates a number of key concepts and ideas elaborated

[41] Marjorie Grene (1910-2009) and Georges Canguilhem (1904-1995) both lived throughout the twentieth century and both demonstrated astute skills in analyzing the history and epistemology of the life sciences. Grene had long been interested in the philosophical approach of Canguilhem (Méthot 2009a) and the two of them met at least once in 1973 in Finland at the "Colloque de Jyvaskyla", an international conference in philosophy where Canguilhem gave his paper on « La question de la normalité dans l'histoire de la pensée biologique ». His talk was followed by a commentary from philosopher of biology Ken Schaffner who rejected Canguilhem's analysis of the concept of normal. Interestingly, while Schaffner, today, does not remember whether Canguilhem answered his commentary, he vividly remembers, however, that Marjorie Grene gave a ten minutes defense of Canguilhem, making him feel that he had been inappropriately critical of the French philosopher and historian (Schaffner, personal communication). This episode illustrates shared concerns between two emblematic, and at the same time atypical, philosophers of the life sciences working on both sides of the Atlantic.

by these earlier thinkers (e.g. phenomeno-technique, recurrence, epistemeological obstacle, and so on), and demonstrates their currency for today's philosophers and historians of science. Moreover, he introduced a new unit of analysis: the *experimental system* (1997; 1994).

Both attempting to bridge the gap between the history and philosophy of science, Rheinberger and Canguilhem are, however, doing so using different units of analysis which do not seem to map neatly onto each other (at least at first glance). And yet, with Rheinberger the standpoint from which to view scientific activity has begun to shift once again, completing the practical and regionalist turn in the history and philosophy of science with the notion of experimental system. To mark the difference in a sharper way Rheinberger himself contrasts his system-centred approach to a concept-oriented one.[42] Illustrating the shift from "concept" to "system" further he insists that his goal is to track the emergence of epistemic things as "material research objects" across a variety of experimental practices, techniques and programmes, "rather than pursuing the developments of *concepts*, disciplines, institutions, or individual researchers" (Rheinberger 2000, 273; emphasis added).

Not only do Canguilhem and Rheinberger promote a different unit of analysis but the latter is primarily concerned with understanding scientific *practices*, "scientific cultures", and overall, to develop an "epistemology of experimentation" (1997, 138; 2005; 2000). In a word, Rheinberger's work is "practice-oriented" and concentrates on the material culture of scientific experimentation – something seemingly remote from Canguilhem's methodology if we think of his approach as being primarily concerned with the elaboration of "genealogies of concepts". Yet as we will see, a deep convergence between these two thinkers emerges once the notion of "concept" in Canguilhem is investigated further.

The difference between Rheinberger and Canguilhem's unit of analysis can be explained by the fact that these authors explored the development of different scientific

[42] For example, Rheinberger claims that in *Synthesising Proteins in the Test Tube* he has "followed the history of an experimental system" (1997, 222), in an attempt to demonstrate "the power of material objects – in contrast to *ideas* or *concepts* – as driving forces in the process of knowledge acquisition" (Rheinberger 2005, 406; emphasis added).

disciplines over different timescales, thus requiring different approaches in terms of narration and analysis. Whereas Canguilhem's interests were mostly located on the side of the history of the life sciences in the eighteenth and nineteenth century, dealing with organisms in their milieu and their interactions, Rheinberger focussed on molecular biology, genetics and more recently, heredity (Müller-Wille and Rheinberger 2007). As a result they both studied different kinds of "objects" that populate those fields: Canguilhem examined how the meaning of concepts such as regulation, health and disease, information or reflex has shifted following their migration through different theoretical contexts; whereas the history of the entities Rheinberger investigated (e.g. microsomes, ribosomes, RNAs) are such that they "cannot easily be reconstructed in terms of *conceptual shifts* that could be considered as being paradigmatic" (2000, 272; emphasis added).[43] On the contrary, the history of such objects results from the establishment of several experimental systems.

Without offering a full argument here, the choice of a unit of analysis for the history of science, I suggest, is contingent upon the temporality of the science at stake, on the one hand, while it also reflects the scope of the narration chosen by the historian and philosopher of science, on the other. Whereas to analyse broad shifts in our understanding of disease ranging from, say, the nineteenth century to the twentieth century "concepts", understood as mediators between practices and other aspects of scientific inquiry, are a relevant units of analysis, detailed case-studies of short-time periods such as the discovery of the genetic code, as Rheinberger showed, require a different approach, one where the emphasis is placed instead on the development of a series of experimental systems. Just as Canguilhem promoted a shift in the unit of analysis in the history of science from Koyré's "ideas" to concepts, particularly when it comes to the life sciences, Rheinberger understood the need for a new unit of narration to make sense of recent and fast growing fields of research such as molecular biology, genomics, and synthetic biology. While neither would claim there is only one correct unit of analysis

[43] As Morange observed, molecular biology occupies only a limited place in Canguilhem's writings, and Canguilhem's analyses of the "molecular revolution" indicate some misunderstanding (2000).

available,[44] both would agree that scientific concepts emerge and shift their meaning within the context of well-defined and localized material and epistemological configurations.

ON THE OPERATIONAL CHARACTER OF CONCEPTS

Following Bachelard, Canguilhem often repeated that "a same word is not a same concept" (2002, 177). Scientific texts sometimes contain terms that are linguistically identical but are nevertheless epistemically different. To distinguish words from genuine (scientific) concepts, Canguilhem tells us, one needs to reconstitute the "synthesis" of a concept, that is, to reconstruct the specific "conceptual context" in which the concept is inserted "and the goal [intentions directrices] of the experiments or observations" (2002, 177). For example, in "Théorie et technique chez Claude Bernard", Canguilhem argued that it is by the means of experimentation in the course of his research on diabetes and with the help of related concepts (such as "internal secretions") and theories (cell theory), that the concept of *milieu intérieur* was formed, not through the application of a "general" scientific method (2002). Going back to the "initial moment" of the creation of a concept like *milieu intérieur* allows to witness the construction of a "properly biological concept, one whose elaboration is at once an effect and a cause of experimentation" (Canguilhem 2008, 7). In other words, concepts are the result of experimentation and foster, at the same time, the developments of new practices. This give-and-take relationship between the construction of a concept and the experimental set-up in which it is embedded opens up new ways of experimentation and vice-versa.[45]

[44] In fact, many other units of analysis could be identified such as, for instance, Keating and Cambrosio's notion of a "biomedical plateform" (2003). While this notion bears similarities with that of experimental system (although it remains distinct from it), fleshing out their precise articulation and specificities requires further study. In fact, the convergence in several trends in historical epistemology is not immensely surprising for Keating and Cambrosio took their PhD in Sociopolitiques des Sciences at the Université de Montréal in the mid-1980s under the supervision of Camille Limoges, himself a former student of Georges Canguilhem at the IHPST between 1964 and 1968 (see Méthot 2009a).

It must also be noted Rheinberger has himself analysed the history of a number of concepts in the spirit of Canguilhem, for instance the concept of gene (2000; Müller-Wille and Rheinberger 2009) and information (Rheinberger 2010).

[45] That is what Canguilhem means when he says that the "concept of the internal environment provides [...] the theoretical foundation for the technique of physiological experimentation" (2002, 148).

Canguilhem rarely expressed himself on the nature of concepts, and we can regret he was not more precise on this issue. We can, however, try to reconstruct his thinking from an article on the concept of reflex in the late nineteenth century where he explains that "when talking about "concepts" he has in mind "a denomination and a definition, that is to say, a noun endowed with meaning that is able to fulfil a function of discriminating between a number of observations or *experiments*" (Canguilhem 2002, 295; emphasis added). Thus for him concepts perform an *operational function* (see chapter 3) as they allow diverse kinds of judgment (e.g. discrimination) to be made. As concepts come into being within certain scientific practices, if one wants to understand the formation, deformation and rectification of biological concepts (as Canguilhem claims), one also has to consider the experimental and material contexts in which they were successively elaborated. This process of conceptual change is indeed not a purely intellectual or theoretical one, well to the contrary. Indeed, the "process of rectification of the concept is not a matter of logic, but of experimentation" (Canguilhem 2002, 296). Concepts are thus both formed *and* rectified in the context of scientific practices.

We could say that the philosophy of Canguilhem is part of a tradition where concepts are "tools"[46] or operational devices used alongside instruments and other kind of scientific apparatuses. For Canguilhem a concept always "contains an operational or judgmental norm" (2005, 198). Paraphrasing a well-known formula, understood in a certain way, Canguilhem's historical epistemology is, somehow, a philosophy of scientific practice and experimentation.[47] Canguilhem's position on the operational character of concepts as depository of norms contrasts with most work on concepts nowadays but many philosophers before him, Kant included, have claimed that concepts are what make judgments possible (see Schmid 2003). It is not surprising that for Canguilhem, reader of Kant, what guarantees the "theoretical efficacy" or the "cognitive value" of a concept is precisely "its operational function" [fonction d'opérateur] (2002, 360).

The point concerning the operational character of concepts was well taken by the French historian of biology and Nobel Prize laureate François Jacob for whom, indeed,

[46] See Feest (2010): Chang (2009).

[47] The experimental aspect of the constitution of concepts in Canguilhem was noted by Barbara (2008).

"the importance of a concept is given *operationally* in terms of its role in directing observation and experience" (1973, 11; emphasis added). The value of a concept thus refers to the possibility of further theoretical, technical, or experimental developments it creates. For example, we could say that Claude Bernard's concept of *milieu intérieur* opened up an epistemic space for the development of physiology as a "deterministic" science, and to do so without drawing on physics as a model (Canguilhem 2002, 149). To recast this point, concepts are not about *representation* alone but also about *intervention*; concepts are at the same time created by the means of experimental practices and later on translated into practice so as to order the messiness of biomedical realities. There is a co-production of concepts and phenomena that takes place inside an experimental set-up. Using Hacking's words, Canguilhem was not interested (only) in how concepts *represent*, but how they *intervene* in the world. Concepts are active, so to speak. The emphasis on the operational character of concepts was recently emphasised by Rheinberger (2010b) as well (chapter 3).

That the (life) sciences can only make significant progress with the right kind of concepts, that is, one that is adequate to their object of study, is roughly the conclusion of Canguilhem's essay on the experimental method in biology: "the use of concepts and intellectual tools forged by that living scientist, the biologist, in order to understand the experience of life proper to the organism is [...] at once both inevitable and artificial" (2008, 22). Not only do concepts operate as tools in observing, measuring, individuating, and studying phenomena, but they can similarly be used to tracing experimentally new "roads", which are by definition artificial, into the living organisms themselves, just like humans' roads cut through their natural milieu. In this resepect, the distinction between an "internal" and an "external" environment provided a means to delineate the phenotypic contours of living beings. On the other hand, experimentation is at once "inevitable" because it partakes to the process of knowledge acquisition which Canguilhem defines as being primarily about resolving the tension between man, life and his milieu, a tension that springs from the requirement to intervene with organisms experimentally to gain access to their modes of functioning, while at the same time recognizing that living organisms are individual (in the sense of indivisible) entities (2008, xix). Forming concepts is no easy task, though, and in biology "the issue is not using

experimental concepts" as such "but experimentally constituting authentic biological concepts" (Canguilhem 2008, 6).

The tightly-interwoven relation between concepts and experimental practices in Canguilhem's epistemology suggests a strong link between the logic of practice as deployed in concept formation and experimentation. But what is the relation between concepts and theories for Canguilhem? Following the "principle of the genealogy of concept", commentators often argued that concepts and theories are, for him, to a large extent decoupled, in the sense that concepts can migrate from one theoretical context to the other (Gutting 2001; Chimisso 2010). Gary Gutting, for instance, commented that "Canguilhem's most important methodological contribution" is precisely the "distinction between concepts and theories" (2001, 229). Drawing on Canguilhem's history of the concept of reflex (1955), Gutting argues that Canguilhem demonstrated how a particular concept can operate within very different theoretical contexts (e.g. mechanism, vitalism), taking on different meanings and significations. For Gutting, Canguilhem's approach posits a neat separation between concepts and theories that allows for the development of a "distinct" kind of history of science, one that is not based on a succession of theoretical frameworks, but on the genealogy of concepts (2006, 8).

The possibility for concepts to move from one theoretical context to another indicates that they are to some extent, independent of theories within which they are invoked.[48] And yet, concepts are not free-floating entities for Canguilhem. The next section will drive this point home drawing on the *Concept of Reflex* and *The Normal and the Pathological*. While Canguilhem's analysis gave precedence of concepts over theories, his more valuable methodological contribution is perhaps not so much the distinction between theories and concepts, but the dynamical logic of concepts formation and scientific practices.

[48] To take a more recent example, the concept of "gene" travelled from Mendelian genetics to molecular genetics and to evolutionary biology shifting meanings accordingly (Beurton, Falk and Rheinberger 2000; Müller-Wille and Rheinberger 2009).

TECHNIQUES AND SCIENCE

Before his "mature" work, the young Canguilhem had already developed a distinctive and original view on the relationship between technique and science that was significantly different from the dramatic discourse on technology pervading the first half of the twentieth century. In effect, at the exact same time Heidegger wrote "The question concerning technology" (1938) in which he worried about the future of a technological society, Canguilhem addressed the problem of technology (or technique) in explicit, but different metaphysical terms in two related articles. His main conclusion is that technological developments do not (necessarily) lead to an instrumental society but rather illustrate a deeper and normative impulse proper to living systems. [49]

In "Descartes et la technique" (1937) and "Activité technique et création" (1938), Canguilhem argued that scientific progress is not a direct result of the *application* of theoretical knowledge (as positivists like Comte would say)[50] but on the contrary, that the growth of science emerges from technical *failures*. Practice, in a sense, discredits theory. In all cases, technique (or technology) is prior to scientific development, both historically and epistemically.[51] For Canguilhem, the development of instruments and techniques as well as their inevitable shortcomings not only facilitates the discovery of new phenomena or the formulation of theories (e.g. Pasteur's germ theory comes from his work on silk worms; thermodynamics comes from the construction of the steam engine, etc.), but opens up future research avenues for scientists to engage into a more theoretically-oriented investigations, precisely because of those unavoidable breaks provoked by technical obstacles (1937, 83-4). Technological development is itself driven by "the exigencies of *life*" [les exigences du vivant], manifesting and extending those deep vital impulses further (1994; 225; 1937, 84; 1978, 72). In a broad Nietzschean sense,

[49] "Human technique extends vital impulses" (Canguilhem 1978, 72). Those vital impulses are attributed by Canguilhem to the whole of life forms: "therapeutic need is a vital need, which, even in lower living organisms (with respect to vertebrate structure) arouses reactions of hedonic value or self-healing or self-restoring behaviors" (1978, 70).

[50] Auguste Comte's slogan was "savoir pour prévoir et prévoir pour pouvoir".

[51] In an essay on "Thérapeutique, expérimentation, responsabilité" published twenty years later (1959), Canguilhem expressed the same idea again, writing that it is "spontaneous technique that creates for knowledge the conditions of its emergence, and thus precedes it" (2002, 387 [1959]).

Canguilhem sees techniques (including medicine and agriculture) as reflecting the "creative" and "original power" of man in his quest to "master" and to become "possessor" of the natural world (1937, 77). Situated somewhere "between life and art", technologies have an irreducible art-like dimension as they are at once both "creative" and liberating" (Canguilhem 1938, 85). Whereas for Heidegger, however, machine-based technology is the hallmark of modernity, technological developments broadly construed express, for Canguilhem, what in *The Normal and the Pathological* he has called the "normativity of life" (1991).

THE CATEGORY OF "EXPERIMENTAL" IN *THE NORMAL AND THE PATHOLOGICAL*

"Medicine is like a technique or art at the crossroads of several sciences" (Canguilhem 1978, 7). This aphorism opens Canguilhem's medical dissertation on the concepts of the normal and the pathological, and is one of the most well-known phrases of the book published in 1943, during the Second World War. *The Normal and the Pathological* (N&P hereafter) can be read from different perspectives, including as a meditation on the concept of biological individuality (Gayon 1998). The category of "experimental" is at the core of the book and supports Canguilhem's argument that the determination of the concept of "normal", especially in physiology and medicine, is linked to specific laboratory equipments and sets of practices; in other words, that there is no absolute concept of the "normal" state in medicine or physiology. Already before Canguilhem developed a more sustained methodlogical reflection to scientific concepts he grasped that their elaboration requires setting up a realm of intelligibility. I first introduce and summarize some of Canguilhem ideas about health, disease, and normativity.

THE POLARITY OF LIFE ITSELF

Medicine, for Canguilhem, is a technique that "extends a spontaneous effort, peculiar to life", the effort of living beings adapting to their milieu, and adapting their milieu to them. Located at the intersection of several sciences, medicine exists "as the art of life" not because therapeutics designates certain states as being normal and others as abnormal, but rather because man, as an individual, has come to call certain dreaded

states as being in need of correction "in relation to the dynamic polarity of life" (Canguilhem 1978, 70). The human enterprise that medicine is reflects thus this "fundamental fact" that life is not indifferent to environmental circumstances, and that it is "polarity" or "position of value", even unconscious (Ibid.) Organisms are normative beings in the sense that, contrary to inorganic matter, they are always affected by their environment and will spontaneously react to external perturbations by making physiological adjustments. Given a change in the environment, healthy organisms will be those that are able to adapt smoothly to the external modifications. For Canguilhem, health is thus defined as "the possibility of tolerating infractions of the habitual norm and instituting new norms in new situations" (1991, 197). Similarly, disease is a "new dimension of life"; it is "an innovative experience in the living being and not just a fact of decrease or increase" (1991, 184). This last point is a critique directed at Claude Bernard's epistemology (which Canguilhem called "Broussais' principle") on which normal and pathological states are identical in nature and only differ quantitatively (i.e. for Bernard, pathological phenomenon amounts to an increase or a decrease of an otherwise normal function). [52]

For Canguilhem, an impoverishment in the plastic or normative capacity is a sign of disease as it indicates a reduction in the "margin or tolerance" at the level of the whole organism. What distinguishes the normal from the pathological then is that an organism will be in a pathological situation if the new norms he has established are inferior in terms of "stability, fecundity and variability of life" than the previous ones (1991, 144). The sick organism is the one which "has lost its normative capacity, the capacity to establish other norms in other situations" (Canguilhem 1991, 183). However, a new norm is never *a priori* normal or pathological; its normality will come from its normativity (1991, 144), that is, from the organism's capacity to organize the *milieu* according to its own needs. In other words, norms of life cannot be said normal or pathological *a priori*, because judgments about normal and pathological states must take into account the environment or the *milieu* into which an organism lives. Grounded in a Darwinian conceptual approach,

[52] Bernard's classical example is diabetes.

Canguilhem argued that "Taken separately, the living being and his environment are not normal: it is their relationship that makes them such" (1991, 143).

The approach just outlined could lead one to think that the frontier between the normal and the pathological may be "imprecise for many individuals considered simultaneously" although, Canguilhem argued, it is "perfectly precise for one individual considered successively" (1991, 182). In this, Canguilhem followed the neurologist Kurt Goldstein and argued that health and disease require the notion of *individual* being. In N&P Canguilhem also argued that physiology cannot secure an objective foundation for pathology because physiological norms are initially noticed through a pathological situation in a clinical encounter (1991, 209). In that, however, he agreed with the French surgeon René Leriche (1879-1955), who maintained that "at every moment there lie within us more physiological possibilities that physiology would tell us about. But it takes disease to reveal it to us" (1991, 100). Although this argument is not a weak one, Canguilhem complements it with a stronger one that brings together scientific practices and concept formation.

THE NORMS OF THE LABORATORY

Canguilhem's strongest argument against the possibility to derive an objective concept of the normal is found in his critique of the science of physiology, and how the laboratory constructs new norms of life that cannot be called "normal" in an absolute sense. Although not frequently mentioned by commentators, "the relationship of the *normal* and the *experimental*", Canguilhem says, "is at the heart of our concerns" (1978, 82; emphasis added). At the outset, N&P critically analyses how the experimental method expounded by Bernard impacted on the ways in which physiology and pathology were being realigned with the clinic at the end of the nineteenth century. For Canguilhem, two important consequences that flew out of these disciplinary rearrangements were that, to begin with, in discovering the laws of normal and pathological phenomenon, physiology became epistemically first, and could pretend to guide and illuminate the clinic. Additionally, in elucidating the statistical constants representing the normal curve of vital functions of living beings, physiology went down a reductionist slope and ended up ascribing health and disease not to the whole organism anymore, but to its most inner

constituents (organs, tissues, cells, etc.) which departed from the statistical mean. Using scientific measurement, health and disease could then be quantified and assessed "objectively". What Canguilhem endeavoured to do in the second part of the book was to turn this view upside down and replace the whole individual, and the clinic, at the centre of medical epistemology.

Canguilhem's concerns in the second part of the book are with the adequation between the norms constructed by the physiologist with the help of laboratory instruments and standardization procedures, and "the living being's functional activity outside the laboratory" (1978, 83). Looking at the distinction between the normal and the pathological from from an evolutionary point of view, Canguilhem frames it as the "problem of the variability of organisms", on the one hand, and the "significance and scope of this variability", on the other (1978, 80). In the context of the physiological experiments, the significance and scope of variability among organisms (and environments) is reduced to a minimum by standardization and control procedures, so that any deviation beyond a particular threshold could be marked as pathological, at least in principle. However, Canguilhem argues, the results from experiments are always context-dependent, as others experimental conditions would have produced other norms.[53] Thus, while the physiologist can claim to have established a norm, he does not "objectively defines which conditions are normal" (1978, 83). And yet, it is the relation between organism and environment that makes them either normal or pathological (Canguilhem 1991, 143). It follows that if one defines the pathological as a deviation from the average, as a statistical difference, the "laboratory's conditions" places the organisms in a pathological situation from which scientists attempt to derive norms understood as the normal state.

A NOTE ON G. CANGUILHEM'S NORMATIVISM

Although Canguilhem denies the possibility for science to objectively identify what the normal is, he does not fall prey to a wholly cultural or social normativism either.

[53] "The living being's *functional* norms as examined in the laboratory are meaningful only within the framework of the scientist's *operative* norms" (1978, 83).

Canguilhem's normativism is intended to be universal and biologically grounded: "even for an amoeba, living means preference and exclusion"; [...] this point of view is that of vital *normativity*" (Canguilhem 1991, 136). This normativity is an intrinsic property of living beings and does not merely reflect social preferences at a given space and time. "The existence, coextensive in space and time with humanity, of medicine as a more or less scientific technique for healing diseases" (Canguilhem 2008, 132) appears to Canguilhem to be the result of a universal tendency in living organisms to avoid diseases and prefer health instead.

> It is life itself and not medical judgment which makes the biological normal a concept of value and not a concept of statistical reality. For the physician, life is not an object but rather a polarized activity, whose spontaneous effort of defense and struggle against all that is of negative value is extended by medicine by bringing to bear the relative but indispensable light of human science (1978, 73).

However, in addition to those biological norms, Canguilhem is perfectly aware that the definition of the normal is partly established by the social context. Technological innovations having considerably enlarged the possibilities of human beings in terms of activities, he argued, the line between the normal and the pathological ought to take into account "certain activities which have become a need and an ideal" for mankind (1991, 200-1). This is why, for Canguilhem, to discern the normal from the pathological one must also "look beyond the body" (Ibid.).

THE FORMATION OF THE REFLEX CONCEPT: APPLIED PHENOMENO-TECHNIQUE

Canguilhem's interpretation of the relation between technique and science feeds back into the formation of concepts by emphasizing the active, even creative role technological apparatuses play. In addition to N&P, the mutually engaging, two-ways relation between scientific concepts, phenomena and technical laboratory apparatuses appears most clearly in Canguilhem's book on the reflex concept where he contrasts the "reflex 1850" with the "reflex 1800". The main difference between these concepts is at

the level of the experimental possibilities generated by the latter, in contrast with the former. As Foucault usefully put it, “The concept of ‘reflex’ was not formed as a biological concept when Willis applied the image of a reflected light ray to an automatic movement; but it did happen the day Prochaska could write it down in the analysis of sensorimotor functions and their centralization in relation to the brain” (1991, 21).

The shift between a word and a concept in the case of the reflex was contiguous to the moment where the tools necessary to measure it and make it happen, so to say, became available. As Canguilhem points out (with an intended play on words), while the concept of reflex 1800 was a “good” concept, it was, however, “not good for anything yet” (1977, 161). The reflex concept was discussed and, indeed, was included in physiology textbooks but no one did anything practical with it yet. Circa 1850, however, things began to change and the reflex concept was not only written in books but “also in the laboratory, in terms of exploratory and demonstrative apparatuses, designed for it, and which would not have existed without it” (1977, 161). In that sense the concept of reflex facilitated the creation of new technical support which, in turn, allowed for a deeper and more thorough analysis of the larger phenomenon of reflex action itself. At this point in time, the reality of the 1850 reflex concept is finally demonstrated “as it brings new objects into existence that it can, in turn, explain” (1977, 161). Concepts and experimental arrangements are reciprocally co-produced.

Drawing on the work of his mentor and friend Gaston Bachelard, Canguilhem points out that the reflex concept in 1850 is no longer “phenomeno-logical” but had become “phenomeno-technical” (Ibid). As early as in *La formation de l’esprit scientifique* Bachelard (1938) had explained that “a concept has become scientific according to the proportion to which it has become technical, to which it is accompanied by a technique of realization” (1969, 61, quoted in Rheinberger 2005, 320-1). Concepts become scientific through their intricate relation with the technical realm. But if the 1850 reflex concept has become more scientific on the grounds that it has become more phenomeno-technique, its validity and usage as a scientific concept is not limited to the frontiers of physiological laboratories. In effect, one find “traces” of the reflex 1850 concept in hospitals, the clinic, but also in the contemporary culture broadly construed (1977, 162-

3). To take a simple but clear example of this, nowadays everyone wants to know "whether they have good reflexes" (Canguilhem 1977, 163).

In an explicit attempt to apply Bachelard's epistemology to biology, Canguilhem relies on the distinction between phenomeno-logic and phenomeno-technique, but he assesses the epistemic value of a concept or a scientific object somewhat differently by examining its "semiotic" insertion in a broader scientific context or culture, and at the changes it brings about at the practical level. For instance, when medical students use a pocket light to detect pathognomonic "signs" most of them ignore who Argyll Robertson is; nevertheless, they construct their diagnosis on the basis of the presence (or the absence) of a reflex action of the eye's accommodation to light. Similarly, the kneecap reflex tested with a small hammer, or the Babinski sign gave the reflex concept at the end of the nineteenth century "the status of a biological fact" to the extent that it becomes unclear whether "its existence realizes a concept" or if it is "its concept that reflects its existence" (1977, 162). The coming into being of the concept of reflex as a "biological fact" is assessed by Canguilhem, finally, not only by the techniques it generated or the instruments it helped developing but also by its "cultural extension", its "public notoriety", that is, by its being rooted in "contemporary culture" (1977, 163).

We begin to understand why describing Canguilhem's approach of concepts as one entirely focussing on the genealogy of concepts is at best incomplete, provided that such interpretation presupposes that the history of those genealogies and their theoretical and experimental backgrounds can be neatly divorced or treated as separate. Because concepts emerge and change, not in the abstract but in the context of concrete scientific practices, this interpretation would be unfaithful to Canguilhem's approach. Thus, one should not talk about genealogies of concepts alone but also of genealogies of *scientific practices* which run an intertwined course. Scientific concepts do not emerge out of nothing and their formation, rectification, and re-organisation are always closely linked to particular experimental cultures, while they also relate in multiple ways to the cultural context in the broader social and political sense of the word.

NO NATURAL HISTORY: DISENTANGLING THE OBJECT OF THE HISTORY OF SCIENCE AND THE OBJECT OF SCIENCE

Hodge's characterization of Canguilhem as being almost obsessed with concepts, truth and rationality is, to be sure, a slightly caricatured portrait, but it does contain a kernel of truth. We have seen in the discussion on phenomeno-tecnhique that Canguilhem does not isolate concepts from theoretical and material contexts, although it is clear he does grant a certain authority to science, which others – like Latour – would certainly like to undermine. In effect, Canguilhem exhibited "a scrupulous respect for the reality of real science", as Louis Althusser put it in the preface to Macherey's 1964 article (1998, 163). Contrary to a number of sociologists of scientific knowledge Canguilhem neither set himself the task to challenge what science tells us about the world or to mount an attack on it based on social, economic or political "influences", nor to explain science by appealing to these very same factors. This respect for science is rooted in the belief that while science is product and part of human culture, scientific discourses and practices cannot, however, be reduced to aspects of a given cultural context. But if one follows Hodge's programme of taking as object of inquiry "nothing other than sources, inventions, influences, priorities, simultaneities, and successions", one fails "to distinguish between science and other aspects of culture" (Canguilhem 1988, 3).

While present and past advocates of historical epistemology are accused of providing a purely internalist history of science, Canguilhem had no illusion that his account was entirely different, for he rejected both internalism and externalism as being deeply flawed. For him "both positions come to assimilate the object of the history of sciences to the object of science" (2005, 202). Science, according to Canguilhem is one of the many cultural systems that flourish within society; but there is something specific, or special about it. Science creates certain norms of rationality that are not found in say, esthetics, politics or culture broadly understsood. To say that science and society are wholly coproduced is to miss this particularity about science that it operates according to a set of norms that are not found outside it. Canguilhem was no naive realist either and recognized that the truth of today in science is often tomorrow's error. For him, the construction of scientific facts does not spring out of unmediated observation of the

world but, as we have seen, is always the result of a configuration of specific technological, conceptual and experimental practices.

A long time elapsed since Canguilhem occupied the directorship of the Institut d'histoire des sciences. His respect for science is nowadays questioned by sociologists like Latour. And yet, Canguilhem's approach can, perhaps surprisingly, help to free the history and the philosopher of science from the tutelage of the scientists, as Alberto Cambrosio, Peter Keating and Alfred Tauber have long emphasized (1994). The subordinate situation occurs when scientists want to impose on historians and philosophers their views as to what really happened in the past of their own discipline. This is a problem that persists today and while calls for "independence, not transcendence" with regard to scientific authority have been voiced (Forman 1991), they were rarely answered or listened to (see Gingras 2007).

Very often, partly because of the (fruitful and important) close collaboration between scientists, philosophers, and historians of science today, the last two are torn between different allegiances (Gingras 2007). The conceptual approach of Canguilhem can help to untangle the situation. Canguilhem's epistemology displays great respect for the sciences and for the scientists who, according to him, tells "the truth" about the world but it offers at the same time a powerful antidote to free both historians and philosophers of science from this subordinate situation, while continuing to acknowledge the specific nature of scientific knowledge and discourses. The reason for this lies in the fact that scientists and historians (and philosophers) of science do not exactly study the same object. Thinking otherwise is to fail to acknowledge that that the history (and philosophy) of science and science are not the same enterprise. As Canguilhem put it, the object of the history of science is secondary, but non-derivative, from the work of scientists, just like the objects of science are secondary, carved out from "nature", without being reducible to it (2005 [1968]). This means that the history of science is no natural history or catalogue of facts, on the one hand, and cannot be reduced to biography, scientists, or scientific results as presented in the many contemporary or older textbooks, on the other (Cambrosio, Keating, and Tauber 1994, 376). As Canguilhem pointed out, scientific objects are "doubly historical" because they are delineated from the work of scientists whose work is itself an attempt to divide-up the natural world into objects, processes, and so on. Scientific

objects, like genes or species are objectified through scientific methods, but are not "out there" ready to be picked out. Just as scientific objects are free from scientific objects, the object of the history of science stands on its own, is defined by the historical method, and does not directly derive from the scientific object itself. Acknowledging that the object of science and the object of the history (and philosophy) of science are distinct provides not only a way to separate both the history and the science, but also for historians and philosophers to re-claim their own disciplinary identity. Both internalism and externalism are flawed because they assimilate the object of the history and philosophy of science to the object of scientific disourses and practices.

The larger implications of Canguilhem's approach become clearer when one looks at the concepts of the life sciences he chose to focus on – health, disease, the reflex, regulation– concepts whose impact reaches beyond science deep into the social and political realms. As a "vital rationalist" (Rabinow 1994), Canguilhem believed that "philosophy must learn from science because only science can tell us what exists" (Canguilhem 1967, 51). This was not a sign of defeat from the part of philosophy; on the contrary, this attitude comes alongside a deep conviction that "philosophy is a normative activity" (Ibid). Canguilhem's position as to the role of science and its relation to philosophy was in sheer contrast with a long philosophical tradition beginning with the Greeks that was still dominant in France in the 1960s and according to which philosophy is primarily a kind of contemplative activity of what is "real". For him, however, the fundamental reason why philosophers should gain a minimal understanding of what scientists take to be real about the world is that it opens up new possibilities as to how this "reality" could eventually be changed. Canguilhem's philosophy, epitomized in his concept of "normativity", is above all a philosophy that leads one to make decision and to undertake action.

François Delaporte once suggested that for Canguilhem, knowledge of life participates of a larger strategy of human beings that leads to a philosophy of action (1993, 228). This is what Canguilhem hinted at in a difficult passage from the essay on Claude Bernard's method already mentioned, weaving together the problem of experimentation, technique and life within a broader action-oriented philosophy: "Experimentation, at the level of its technique, contains a philosophical theory of the life

sciences that relates itself to a philosophy of action of the science on life" (2002, 154). It is no coincidence that the concepts studied by Canguilhem are core concepts of the life sciences. In fact, Canguilhem's project could be summarized as one constantly attempting to come to terms with advances in biomedicine by demonstrating how the formation of concepts is one of the multiple forms of living. Or, As Foucault poignantly noted in a tribute article to his mentor: "forming concepts is one way of living, not killing life" (1991, 21).

Not only do the evolutions of concepts partake of an experimental culture but they also constitute a platform onto which broader relations of power are articulated. The link between power and knowledge embedded in scientific concepts was developed further by Foucault but can already be identified in Canguilhem's work. Although concepts are linguistic entities to which we attach different meanings, they are not just "words", that is, they are not neutral descriptions of scientific objects – they also convey value judgments about people, society, and so on. As Staffan Müller-Wille recently emphasised, "the meaning of a concept [for Canguilhem] does thus not exhaust itself in its discursive relationship to other words and texts only"; on the contrary, concepts "articulate dynamic power relationships of authority and resistance by advancing certain evaluations in order to contest or overcome others" (2011, 479). For example, the 1850 concept of reflex, spreading across many disconnected fields, served the purpose of those promoting a mechanistic philosophy of labour where the actions of the workers are decomposed into smaller reflex actions in order to fit larger economical needs in the production of goods. Following the analysis of G. Friedman, Canguilhem remarked that the reduction of the worker's actions to a "sum of reflex" was only possible once man in general was assimilated to a (no doubt complex) machine, as for example in Taylorism, and his actions subordinated to it. As Canguilhem concluded, however, "in so far as the worker refuses practically to be mechanised, he brings to the fore the theoretical error consisting in decomposing his own actions into mechanical reflexes" (1977, 166).

CONCLUDING REMARKS

This chapter was concerned with a neglected aspect of Canguilhem's historical epistemology, namely the links between the formation of concepts, scientific practice,

and technologies. The motivation behind it was that on the one hand there seems to be a widespread misunderstanding of what a "concept" is, and that, in turn, led to some confusion and some criticisms of Canguilhem's conceptual approach. I hope the previous analyses provided a new perspective on Canguilhem's epistemology that breaks with the image of him as being a philosopher of disembodied concepts. Despite the fundamental role of concepts in both science and its history, Canguilhem rarely explained what a concept is, and what the nature of a philosophy of science based on the analysis of concepts could possibly mean. Philosophers and historians have tended to assume that the notion of a "concept" in Canguilhem's writings was straightforward and transparent, and some crucial aspects of the formation of concepts have been overlooked, caricatured, or simply ignored over time such as the relation between concept formation and various epistemic practices. As a consequence, concepts in Canguilhem's philosophy have somehow become understood as free-floating entities, with no connection whatsoever to either experiment or theory. This idealized history of science was further accused of neglecting the role of institutions and influences in the growth of science. The previous sections illustrated that, on the contrary, the formation of biological and biomedical concepts is always grounded in a set of experimental practices. It was shown that the kind of epistemology Canguilhem provided is one deeply embedded and embodied in concrete scientific practices, where experimentation has a privileged place. As a consequence, if one wants to talk about a genealogy of *concepts* as a sound methodological approach for the history of the life sciences, one should do so by linking it to a genealogy of experimental *practices* that accompany them and operationalize them in various ways.

To come back to the criticisms of conceptual history described at the beginning of the chapter, Hodge's point of contention was that the "concept" is not a relevant unit of analysis for the history of science because it is a "product, an achievement, not a process or a goal" (2000, 72). We have seen, however, that concepts cannot easily be grasped as "product" because they are changing and morphing entities. To use a more recent label, scientific concepts are often "in flux" and this is precisely what makes them interesting entities to study scientifically, historically and philosophically (chapter 3). Concepts can become "achievements" in Hodge's sense – for instance, the "reflex 1850" – but only temporarily before they go through another round of rectification process.

As to Latour's critical remarks, suffice it to say here that firstly, as Mary Tiles recently observed, there is no doubt that historical epistemology is closer to social and political concerns than most of what is done in "epistemology" in the Anglo-American world in particular and in the philosophy of science more generally (2011). Secondly, although Canguilhem never exposed scientific knowledge as being "socially constructed", his work showed that a number of key concepts such as regulation, disease or reflex, which are apparently neutral, are in fact value-laden and have significant impacts on social norms. Nowadays the label historical epistemology is commonly used to characterize very different thinkers including Husserl, Cavaillès, Fleck, Bachelard, Canguilhem and Foucault, and a plurality of research projects such as Daston's, Renn's, and Rheinberger's. What seems to unite most of these projects is the emphasis placed on the need to historicize epistemological categories which were once taken for granted, while at the same time avoiding the trap of relativism or social constructivism.

Finally, how can we reconcile Canguilhem's disavowal for the label of historical epistemology with the strong intuition that it is the most compelling way to describe Canguilhem's approach? As indicated above, if we accept Gingras' account of historical epistemology as being primarily a philosophical project, there is no reason *not* to include the work of Canguilhem under this categorization. But there is another way to look at it. According to the interpretation of Rheinberger in *On Historicizing Epistemology* (2010b) historical epistemology is not a concerted "research programme" and is not reducible to the work of a few isolated individuals. Historical epistemology captures a deep trend in the history of philosophy of science itself, one that includes the work of Canguilhem. Under the heading of historical epistemology, Rheinberger brings together a deeper, double movement of the "historicization of the philosophy of science" and the "epistemologization of the history of science" starting in the late nineteenth century science and continuing throughout the twentieth century (2010b, 3-4). In replacing Canguilhem's contributions within this larger historical perspective and in reassessing his philosophical legacy it is hoped that his work will continue to stir the development of historical epistemology on both sides of the Rhine and beyond to create a genuinely integrated approach to the history and philosophy of science.

CHAPTER 2: DARWIN, EVOLUTION, AND MEDICINE: HISTORICAL AND CONTEMPORARY PERSPECTIVES

INTRODUCTION

Centenary commemorations provide long-awaited opportunities to explore the influence of scientific ideas, concepts, and methods developed previously, but also allow deconstructing myths and revisiting historical claims, or omissions. Monographs commemorating the work of Charles Darwin (1809-1882) typically embrace a wide range of topics on which the theory of evolution has thrown some light, but the influence of Darwinism in medicine and the health sciences was until recently often left out in the dark.[54] The essays gathered in *Darwinism and Modern Science* (1909), published on the occasion of Darwin's hundredth birthday and the fiftieth anniversary of *On the Origin of Species* (1859), for instance, explored how the theory of evolution impacted on other branches of the natural and social sciences, including philosophy and history, but did not touch upon the topic of health and disease. At least one physician addressed the question directly this year, however. In his Bradshaw lecture on "Darwinism and Medicine", J.A. Lindsay, working at Queen's University in Belfast, considered the "significance of Darwin's great discovery for medical thought and practice" (1909, 1325). Musing on the nature of disease, Lindsay concluded that it [disease] "becomes something more than a disagreeable and embarrassing fact when we realize how closely it is related to evolutionary processes". Disease, he continues, "even takes its place – a temporary place we may hope – in the eternal order" (1909, 1331). *Evolution in the Light of Modern Knowledge* published a few years later (Bateson and Seward 1925) contained no contribution on medicine and evolution either, however. This neglect was noticed by a professor of pathology in London who, one year later, wrote an essay in *The Lancet* entitled "Disease in the light of evolution" in the hope "to supply the missing chapter" (1926, 1075).

[54] See Bateson and Seward (1909).

The second important commemoration of Darwin's work marked the centenary of the publication of *On the Origin* in 1959 appeared to have had equally little to say about the relations between evolutionary biology and medicine.[55] Yet evolutionary biology has crossed path with medicine more than once during the last 150 years, although the changing nature of these interactions has only begun to be addressed historically and philosophically (Zampieri 2009a; Zampieri 2009b; Bynum 2002; Bynum 1983). In 2009, however, the question as to how do Darwin's theories relate to medicine historically, and what the relations between the medical sciences and evolutionary biology are today, was at the center of numerous workshops held worldwide and was, at the same time, the focus of several scientific publications in medical journals.[56] In fact, since more than twenty years the nature and causes of health and disease are increasingly being addressed in the light of evolution, a shift that indicates a global change in both the public and scientific perception of the role of evolutionary biology in medicine and the health sciences broadly construed.

While the progressive growth of mechanistic explanations of disease can be regarded as "one of the most salient features of the development of medicine over the past three centuries" (Tracy 1992, 53; Campaner 2011), we have recently witnessed rapid developments in evolutionary explanations of disease (Williams and Nesse 1991, Nesse and Williams 1996; Stearns 1999; Trevathan et al. 2008; Stearns and Koella 2008; Gluckman et al. 2009). This current trend is reflected in a number of international conferences that aim to assess the medical consequences of the evolutionary past of human beings and to negotiate a space for the teaching of evolution in medical schools (see Nesse et al. 2010). Sometimes these evolutionary perspectives go under the heading of "Darwinian medicine", but occasionally, the term "evolutionary medicine" is used instead. This is done on the grounds that the term Darwinian medicine narrows the

[55] In a lengthy essay Smocovitis (1999) relates the organization of the 1959 centenary in the United States by the Darwin Centennial Committee. To the exception of Ilza Veith who was from the department of medicine and was interested in the history of medicine, the other committee members were from the departments of zoology, geography, and paleontology. Veith's own contribution to the centenary, however, was not on medicine but on "Creation and Evolution in the Far East" (Smocovitis 1999, 318).

[56] See *The Evolution and Medicine Review* (online), and the contributions in the special issue in *The Lancet*, December 2008.

concept of evolution to the processes of natural selection and adaptation while evolutionary medicine is more general and acknowledges other important aspects of the theory of evolution such as symbiosis, the role of epigenetic processes, and so on (Swynghedauw 2004; Lewis 2008). However, the nomenclature is not firmly established, and often, the expressions are used interchangeably (Zampieri 2009b, 347).

As one of my goals for this chapter, I defend a methodological distinction between two evolutionary approaches that I have sketched elsewhere (Méthot 2009; 2011). I think that the terms Darwinian medicine and evolutionary medicine are useful for expressing the contrast between the two orientations. I follow Stephen Lewis (2008) in drawing this distinction, but in contrast with Lewis, what I propose is informed by David Buller's distinction between Evolutionary Psychology as specific to the work of John Tooby and Leda Cosmides and evolutionary psychology broadly construed (Buller 2007, 256). Buller's distinction is important because it permits the distinctiveness of the former to be characterized and contrasted with other kinds of biological explanations of human behaviour, which involve evolutionary biology, such as evolutionary anthropology or human behavioural ecology. Similarly, I want to argue that distinguishing evolutionary from Darwinian medicine will help us assess the variety of roles that evolutionary explanations can play in a number of medical contexts. Because the boundaries of evolutionary and Darwinian medicine overlap to some extent, however, they are best described as distinct "research traditions" rather than as competing paradigms.[57]

In this chapter, I focus especially on two styles of evolutionary explanations of disease in order to render more precisely the distinction between these two research traditions. I begin by drawing a contrast between evolutionary and Darwinian medicine. Then I give a more fine-grained critical description of the field of Darwinian medicine. Finally, I show that evolutionary and Darwinian medicine can also be distinguished with respect to the styles of evolutionary explanations they employ. Whereas the former

[57] Recently, Nesse suggested that "in order to provide a designation as general and inclusive as possible" he prefers to call the field neither Darwinian medicine nor evolutionary medicine but "evolution and medicine" (2007, 419). Terminology aside, my distinction is intended not to promote a division of labour among practitioners but rather to draw attention to the different methodological principles and underlying assumptions that guide research in this area, in addition to some possible historical connections with older research traditions.

primarily involves "forward looking" explanations, the latter depends mostly on "backward looking" explanations. A forward looking explanation tries to predict the effects of ongoing evolutionary processes on human health and disease in contemporary environments (e.g., hospitals). In contrast, a backward looking explanation typically applies evolutionary principles from the vantage point of the evolutionary past of humans (here, the Pleistocene epoch) in order to assess present states of health and disease among populations. The contrast between these two explanatory styles can also be captured by the distinction between a theoretically and a practically oriented approach; whereas evolutionary medicine seeks to devise practical solutions to medical problems based on specific applications of evolutionary biology's toolbox, Darwinian medicine, in contrast, stresses the need to compare past and present populations from an evolutionary point of view in order to gain insights into why we in the present get sick. Both approaches, however, are ultimately concerned with the prevention and control of human diseases. To illustrate how forward looking explanations can work I develop the example of the evolution of antibiotic resistance. First, however, I provide an overview of the relations between the history of Darwinism and medicine in order to contextualize the recent development of Darwinian and evolutionary medicine.

CHARLES DARWIN AND THE DOCTORS

Despite not being a doctor himself Charles Darwin had "medicine in his blood", so historian of medicine William Bynum said (1983, 43). Indeed, the young Charles may have dropped out of his medical studies in Edinburgh (1825-1827) to study theology in Cambridge and later natural history, but he grew up in close contact with medical doctors, including his own father and grand-father, the colourful Erasmus Darwin. During most of his professional life Darwin's friends and scientific correspondents included many doctors like Henry Holland, John Scott Burdon-Sanderson, William B. Carpenter, Lawson Tait, and James Paget (Towers 1968). Darwin's own experience with chronic, but intermittent, illness resulted in his frequently undergoing various medical treatments.[58] Toward the end of his life Darwin was pleased to bear witness to the development of one

[58] The nature and cause(s) of Darwin's illness have been the focus of much speculation and are still debated nowadays. For a recent view see Hayman (2009).

of medicine's most powerful theory: the germ theory of disease, as developed by Pasteur and Koch. In a letter to botanist and bacteriologist Ferdinand Cohn in 1877, Darwin wrote:

> I remember saying to myself, between twenty and thirty years ago, that if ever the origin of any infectious disease could be proved, it would be the greatest triumph to science; and now I rejoice to have seen the triumph (quoted in Bynum 1983, 52).

Whilst the development of the medical sciences during the nineteenth century had relatively little impact on Darwin's own scientific work, the converse is not true – indeed quite to the contrary. As the London physician K.W. Millican indicated in his monograph on *The Evolution of Morbid Germs*, "the general application of the great doctrine of evolution to disease appears to have been more or less distinctly 'in the air' for some considerable time" (1883, 44). More precisely, and as Bynum rightly noted (1983, 46), medical practitioners rapidly turned to Darwin's evolutionary theory and to his work on heredity (Darwin 1868) to understand both the "diseases of evolution" (hereditary diseases) and "the evolution of diseases" (infectious diseases). Drawing on the *Origin of Species* epidemiologists and public health officers relied, on the one hand, on the concepts of natural selection and adaptation to explain the remarkable virulence seen during epidemics in terms of ongoing evolution (or lack thereof) between hosts and microorganisms (Thorne Thorne 1882; Airy 1878), and those concepts also provided early bacteriologists a way to reconcile the observable and sometimes puzzling variation in infectious diseases with the claim that diseases have a specific cause (e.g. a bacterium).

On the other hand, physicians and surgeons who studied the transmission patterns of specific pathologies from one generation to the next, and how these traits sometimes disappear, revert, and suddenly reappear in a discontinuous but heritable fashion in offspring, emphasized yet another aspect of Darwin's work, namely his theory of heredity, or pangenesis (Paget 1883; Hutchinson 1884; Bland-Sutton 1890; Haycraft 1894). For, building on the breeders' knowledge of inheritance and on Prosper Lucas's (1805-1885) *Traité philosophique et physiologique de l'hérédité naturelle* (1847), Darwin's *Variation of Plants and Animals under Domestication* (1868) supported the view that

inheritance can be adaptive as well as maladaptive, as hereditary diseases indicate. This is but one aspect of the "dark side" of evolution which remains an underappreciated aspect of Darwin's work even today (Müller-Wille 2009).[59] In addition, old medical concepts of constitution, predisposition to disease, and diathesis were, at the time, reinterpreted from an evolutionary point of view as well (Zampieri 2009a). Diseases of evolution also included "disease of modern life" which would later be called "diseases of civilization". [60] On the whole, unraveling the genealogical trajectory of diseases through Darwinian concepts provided a new understanding of a number of pathologies, social or otherwise, in the late nineteenth century.

Although one should not draw the line between the "evolution of diseases" and the "diseases of evolution" too sharply – indeed, germ theorists also believed that pathogenic germs can undergo "reversion" and "atavism" – late nineenth century medical scientists appear to have applied Darwin's theories to medicine to two broad lines of thinking (Bynum 1983). Moreover, one can trace significant continuities between these two ways of understanding the role of evolution in medicine and today's Darwinian and evolutionary medicine: the former inquiring into the origins and nature of humans' adaptations (and maladaptation) and their hereditary transmission, and the latter focusing on the factors influencing the evolution of infectious diseases. Like their analogues in the late nineteenth century, these new evolutionary trends to disease and health sometimes overlap while they also bear the marks of older research traditions from which they derive.

DARWINISM AND EUGENICS

The period spanning 1880 to 1940 – recently labeled the era of "medical Darwinism" – saw the publication of a large number of medical articles, books, reviews, and letters on "Darwin", "Darwinism" or "evolution" in leading journals such as the *British Medical Journal* and the *Journal of American Medical Association* (Zampieri 2009a). This flow of publications, however, radically came to a halt in the aftermath of the Second World War,

[59] The most direct application of Darwin's theory of inheritance to disease is Ross (1872) and his graft theory of disease which he based on the hypothesis of pangenesis.

[60] See Benjamin Ward Richardson's *Diseases of Modern Life* (1889).

save for a noticeable peak in the mid-50s on the occasion of the centenary of the publication of *On the Origin of Species*. It will have escaped no one that eugenics – the idea of artificially selecting for (or against) specific (presumably) heritable traits among human populations – was a major force in shaping the relations between the medical sciences and evolutionary biology from the publication of Darwin's *Origin* until the mid-1940s and beyond (Harwood 1989). The idea of an organized selective mating process emerged, and gained wide acceptance, within the particular context of Victorian society, in which scientists, lay persons, and politicians of all allegiances expressed concerns about the forces of degeneration they perceived to act on the mental, the physical, and indeed the moral, abilities of individuals. In Britain, but also outside it, a large fraction of the population regarded rather anxiously the long-term impact of medicine on the preservation of the "less-fit" (e.g. the so-called "feebleminded"), as much as they feared its larger effects on the economy, politics, and society writ large.

The then-perceived consequences for society of tampering with the law of natural selection weeding out ill-adapted or diseased individuals, and permitting them instead to live and to reproduce, were regularly addressed from a medical point of view. For instance, in 1869 the Birmingham surgeon Lawson Tait (1845-1899) asked whether "the law of natural selection by survival of the fittest failed in the case of man".[61] Tait, a pioneer of ovarian surgery, corresponded widely with Charles Darwin whose theories he painstakingly sought to support through his own medical work (Shepherd 1982). In his 1869 essay, however, Tait was primarily concerned with the apparent tension that "medical science enables the diseased to live, those whom it saves from dying prematurely it preserves to propagate dismal and imperfect lives" (Tait 1869). Darwin was not estranged to these discussions although he did not himself encourage the practice of eugenics. In *The Descent of Man* (1871), he expressed the same concerns as those voiced by Tait and others before him about the effects of a prolonged relaxation of natural selection – partly made possible thanks to medical advances (e.g. small-pox vaccination) –

[61] The possibility that natural selection does not operate in human societies was already addressed a year earlier by William, R. Greg in a polemical essay "On the failure of natural selection in the case of man (1868). This essay, not written by a medical man, contains remarks that parallel Tait's reasoning. For instance, Greg notes in his conclusion that "medical science is mitigating suffering, and achieving some success in its warfare against disease; but at the same time it enables the diseased to live" (1868, 362).

for the march of societies toward progress (1871, 168). However, and in contrast, Darwin noted that the sympathy instincts that lead us to give protection to the "imbecile, the maimed, and the sick" are themselves the product of evolution by natural selection, and suppressing those instincts would be impossible "without deterioration in the noblest part of our nature" (1871, 168-9).

In 1869, Francis Galton (1822- 1911) – who was Charles Darwin's cousin and who coined the word "eugenics" in 1883 – published *The Hereditary Genius*, a very influential book in which he inquired into whether human abilities were heritable, separating for the very first time the realms of nature and culture, and stressing, against Darwin, the "unity of type" over individual variations. Faithful to his eugenics utopia, Galton saw the use of artificial selection as the easiest and quickest way to achieve what natural selection would eventually realize (Gayon, forthcoming). Some medical men had more temperate views on how one should envision the relations between evolution and the medical sciences, however. In his Bradshaw Lecture on "Darwinism and Medicine" delivered at the Royal College of Physicians in 1909, J.A. Lindsay raised doubts regarding the ability of doctors to effectively control births and maintain "the purity of the race". Amidst subtle ethical overtones he warned, though, that "the possibility of reversion and degeneration will always have to be reckoned with" (1909, 1331). A few years later the biometrician and then-director of the Francis Galton Eugenics Laboratory in London, Karl Pearson (1857-1936), gave a Cavendish lecture at the West London Medico-Chirurgical Society titled "Darwinism, Medical Progress, and Eugenics". In his talk, Pearson did not hesitate to argue that Darwinism and medical progress are radically "opposed forces" and that the tension between them could indeed only be resolved through the implementation of strict eugenics policies of birth control (1912, 27).

With the rediscovery of Mendel's laws of inheritance circa 1900 and the beginning of genetics Pearson's project of birth control became to a large extent a social and political reality for countless individuals.[62] In effect, at the turn of the twentieth century positive and negative forms of eugenics practices (e.g. sterilization laws) blossomed in several

[62] Pearson, however, was fiercely opposed to Mendelian genetics. On the debate between biometricians and Mendelians see Olby (1988).

North American and European countries, including the United States, Canada, Sweden, Britain, and Denmark (Kevles 1985). When the association of Nazi crimes during the Second World War with a number of eugenics movements was brought to light, the application of Darwinian concepts to "medical" questions became for a time morally untenable, at least publically. Possibly, *this* is the main cause of the discernible "oblivion" of evolutionary approaches to medicine in the second half of the twentieth century (see Zampieri 2009a, 24).

Eugenicist concerns with racial degeneration, though publically dismissed, did not disappear at once after the war and the revelation of the concentration camps; such concerns continued to be promulgated by prominent medical scientists and geneticists until the 1960s in the United States, Britain, and Germany (Paul 1984), but also elsewhere, and afterwards. The Australian immunologist and Nobel Prize Winner Frank Macfarlane Burnet (1899-1985), for instance, expressed strong eugenicist opinions, not too dissimilar from those of Pearson and others before him, during a symposium on The Impact of Civilization of Man held in Canberra in 1968. As the chairman of the meeting Burnet argued that given the social patterns in today's society there was no hope of avoiding "genetic deterioration", and consequently scientists would fail their responsibilities if "opportunities for rational birth control are not made equally effective through all classes of all human communities" (1970, xvi-xix).

Forty years on, while new work in genetics and genomics is giving rise to further medical applications such as pre-natal testing, genetic screening for various hereditary diseases, and so on, attempts are frequently made to separate the new genetics from the old eugenics (see Hansen, Janz, Sobsey 2008). Yet while the new genetics is often branded as being individually empowering, medically predictive, voluntary, protective of individual rights, and based on accurate science, it is not always possible to demarcate it sharply from old eugenics (Ekberg 2007). In the light of the complex and problematic history of medical progress and evolutionary thinking during the twentieth century, it hardly comes as a surprise that one of the constant challenges faced by any kind of evolutionary approach to health and disease nowadays is to safely distance itself from this eugenicist past. Randolph Nesse and George Williams were fully aware of the potential misreading of their project when they labeled it "Darwinian medicine" (Williams and Nesse 1991). As

they wrote, one of the main obstacles for physicians to embrace an evolutionary perspective is that "of course, whenever evolution and medicine are mentioned together, the specter of eugenics arises" (Nesse and Williams 1998, 92). Although eugenics was certainly a powerful factor, both in making and dissolving the relations between medicine and evolutionary biology, more subtle evolutionary approaches to disease have crossed the twentieth century, relatively unaffected by the political turmoil (chapter 4, 5). In subsequent sections I will instead try to depict how the relations between evolutionary biology and medicine were remade once again from the early 1990s onwards and how we can detect significant historical and conceptual continuities between these new research projects and the way in which Darwin's work was read by medical doctors in the late nineteenth century.

EVOLUTIONARY MEDICINE

Evolutionary medicine is the study of the evolution of diseases, to use Bynum's terminology, and it focuses on the large and increasing number of illnesses that evolutionary biology's conceptual and methodological resources can shed some light on. Typical examples include the evolution of infectious diseases, antibiotic resistance, the evolution of virulence, etc. In that sense, evolutionary medicine has a long tradition that predates the birth of Darwinian medicine by many decades. Indeed, although Charles Darwin himself said little about medicine per se, evolution-oriented accounts of infectious diseases, for instance, were progressively advanced by medical doctors and epidemiologists a few decades after the publication of *On the Origin of Species*, as discussed above (Bynum 1983). On this view, germs that cause disease result from long evolutionary processes through which they have progressively acquired (or lost) their pathogenic power. Similarly, *in vivo* laboratory experiments provided evidence that changes induced in microorganisms were heritable. In this sense, Louis Pasteur's laboratory experiments on variable virulence in bacterial strains could also be regarded as an early example of evolutionary medicine, where evolutionary thinking provided new ways of intervening on disease, for instance, by controlling the level of virulence in the production of standardized vaccines (Mendelsohn 2002). Across the twentieth century, attempts to understand the origin, evolution and decline of infectious diseases from

various viewpoints such as bacteriology, molecular biology, or ecology underline the history of evolutionary medicine from the late nineenth century up to the present day.

As I see it, evolutionary medicine does not stand out as a new scientific field of its own, however. To put it differently, evolutionary medicine is not a theoretically unified scientific domain but, rather, a collection of different research agendas. Scientists doing evolutionary medicine draw on different fields such as population genetics, microbiology, bacterial genetics, ecology, immunology, and, of course, evolutionary biology to understand and regulate medical problems. Accordingly, today's evolutionary ecologists and epidemiologists interested in the dynamics and ecology of infectious diseases, emergent diseases (e.g., HIV-AIDS, H1N1 flu, Ebola virus, etc.), and host-pathogen coevolution are engaged in evolutionary medicine, sometimes without knowing it. It would therefore be a mistake to think that evolutionary medicine has a strong internal cohesion in terms of epistemology and methodology. Applying Buller's description of evolutionary psychology, evolutionary medicine is not a synthesis but, rather, "a loose confederation of research programs that differ significantly in theoretical and methodological claims" (2007, 255).

What is central, though, is that in this broader sense, evolutionary theory is employed to provide an additional axis of research to medical researchers, health care practitioners, clinicians, policy makers, and others. What unites evolutionary medicine is mainly the attempt to articulate questions about health and disease with concepts and methods drawn from evolutionary biology in order to devise practical solutions to pressing medical problems. Evolutionary biology provides medicine with an additional level of explanation for disease that can lead to new technological applications, not a broad theoretical worldview as to why we get sick. In applying evolutionary principles in contemporary environments, for example, in hospital wards, intensive care units, and so on, evolutionary medicine seeks to address "real time" evolutionary issues of medical significance such as the prediction and control of the evolution of infectious diseases or the evolution of resistant bacterial strains. In that sense, evolutionary medicine is characterized by what I call a "forward looking" mode of evolutionary explanation.

DARWINIAN MEDICINE

There is a more unified tradition of evolutionary studies of medicine called "Darwinian medicine", however. As mentioned above, this tradition is recent and began with the work of psychiatrist Randolph Nesse and evolutionary biologist George Williams in the early 1990s. It is now pursued by Stephen C. Stearns, Stanley. B. Eaton and others. Although this tradition is more recent, it also has historical roots and predecessors in the late nineteenth century and early twentieth century biology. Indeed, Darwinian medicine, at least as initially conceived, is in many ways analogous to the study of diseases of evolution in the late nineteenth century. Today, practitioners use the neo-Darwinian theory to understand the genealogical patterns of disease transmission; to determine why individuals are, or become, maladjusted to their environment; and to provide an evolutionary explanation of disease susceptibility framed in terms of our evolutionary past. Understanding patterns of disease in the light of the evolutionary trajectory of humankind stands out as a distinctive feature of Darwinian medicine and reflects its historical origin in one of the late nineteenth century answers to Darwin's work.

Whereas the forerunners of Darwinian medicine during the second half of the twentieth century were largely unsuccessful in promoting evolution-based medicine among larger audiences, Nesse and Williams's *Evolution and Healing: The New Science of Darwinian Medicine* (Nesse and Wiliams 1996 [1994]) rapidly gained worldwide recognition. Nesse and Williams' approach to disease benefited from several recent developments in medical genetics and medical anthropology. Given that their work drew on the work of Harvard evolutionary biologist Edward O. Wilson, who attempted to apply evolutionary principles to human behaviour, it is unsurprising that questions about human evolution, behaviour, and psychology were often intertwined in Darwinian medicine.

In contrast with evolutionary medicine, Darwinian medicine is united by a number of distinctive theoretical and methodological claims that can be summarized as follow:

- Adaptationism (methodological) is a good heuristic principle in medicine;
- Functional and evolutionary explanations must be systematically articulated in order to understand vulnerability to disease;
- Evolution provides medicine with an organizing theoretical framework, and the

potential domain for the application of evolutionary principles is unbounded;
- Evolutionary principles are applied from the vantage point of the Pleistocene epoch (backward looking explanations);
- Humans are generally maladapted to the modern environment (the mismatch hypothesis).

In what follows, I will consider the first three claims one-by-one and then the fourth and fifth claims jointly.

AN ADAPTATIONIST PROGRAM

Following the evolutionary biologist Stephen J. Gould and population geneticist Richard C. Lewontin (1979), Williams and Nesse have described Darwinian medicine as being an "adaptationist programme" [1991, 3). Darwinian medicine's adaptationism is primarily methodological. A methodological adaptationist assumes that "looking first for adaptation is a useful research strategy" (Forber 2009, 156). In other words, it is "a suggestion about how […] best to organize investigation" (Godfrey-Smith 2001, 338). Williams and Nesse seem to satisfy the condition for being methodologically adaptationist by making the following recommendation: "When confronted with a biological phenomenon, try to envisage it as an aspect of an adaptation" (1991, 3). Applying this research strategy to medicine, they argue that "the adaptationist program predicts otherwise unsuspected adaptive processes" to be medically significant (1991, 3; Nesse and Williams 1996, 21).

In effect, methodological adaptationism leads to the reconsideration of the nature of a number of pathological reactions. One of Darwinian medicine's central claims is that "many manifestations of illness are not defects in the body's mechanisms, but sophisticated adaptations" (Nesse 1999, 353). This adaptationist stance is intended to provide a new way of looking at symptoms of bodily disease (e.g., pain, fever, iron deficiency, etc.) or mental disorder (e.g., panic attack, depression, etc.). Instead of thinking about these conditions in terms of symptoms of a disease, adherents of an adaptationist perspective stress instead their selective advantage (Nesse 1999). All this suggests a practical role for adaptationist thinking in clinical medicine (Nesse and Williams 1996, 245–48). In effect, Williams and Nesse have argued that "clinical practice will also

benefit from an evolutionary perspective" in the sense that evolutionary theory has "immediate practical utility when considering what to do about a low iron level in a person with a chronic infection, whether to suppress cough in a person with pneumonia, or when to adopt new technology" (1991, 17). For Williams and Nesse, "the adaptationist" doctor is thus better equipped to understand why diseases occur (ibid.).

Treatment of disease, however, is unlikely to rest on evolutionary considerations alone (Gammelgaard 2000), as Darwinian medicine's advocates themselves now recognize (Nesse and Stearns 2008). For instance, deciding whether or not to block fever will depend on a constellation of factors which are only very loosely related to the fact that fever is an evolved mechanism. In choosing to suppress fever, the nature of the disease and the patient's sex and age—in addition to his general state of health and other conditions—are arguably of greater relevance than evolutionary knowledge. In cancer, for instance, fever is commonly associated with a high mortality rate (Dalal and Zhukovsky 2006). Although the benefits of applying adaptationist thinking to clinical medicine will require some more empirical work, Williams and Nesse rightly point out that it can lead physicians to better "appreciate compromises that are responsible for much disease" (1991, 17). Overall, Darwinian medicine rarely offers practical guidelines; its aim is to guide research instead (Nesse and Stearns 2008, 31).

FUNCTIONAL AND EVOLUTIONARY EXPLANATIONS OF DISEASE VULNERABILITY

The goal of Darwinian medicine is to gain a better understanding of why members of our species get sick and to do so from an evolutionary standpoint (Nesse and Williams 1996). In other words, Nesse and Williams wonder why the body is not better designed; why has natural selection left us vulnerable to disease? Using Ernst Mayr's terminology (Mayr 1961), they argue that functional (or proximate) biology does not suffice to explain disease, and so they urge that "each disease needs a proximate explanation of why some people get it and others don't, as well as an evolutionary explanation of why members of the species are vulnerable to it" (Nesse and Williams 1998, 93). The case of sickle-cell anaemia is one of the clearest examples that bridge the gap between evolutionary and functional (or proximate) explanatory schemes. This emphasis on disease vulnerability is one of the most salient aspects of this research tradition. The idea is that "natural

selection shapes structures and functions that, being imperfect, are vulnerable to disease" (Zampieri 2009b, 348).

Nesse and Stearns have distinguished six main reasons for disease vulnerability (2008), each one couched in terms of what natural selection can and cannot achieve. First and foremost, natural selection cannot (1) overcome the mismatch between genes inherited from the Pleistocene and modern environments because the response to selection is too slow. The speed at which selection operates also explains why (2) pathogens continually find ways to circumvent our evolved defences. A number of (3) structural constraints and (4) historical trade-offs limit what natural selection can do to decrease disease vulnerability. Finally, the authors argue that natural selection (5) maximizes fitness, not health, and (6) that a number of defences like pain and fever "are useful despite causing suffering and complications" (2008, 38). In brief, disease is not something that can be completely avoided and pathological situations are sometimes the inevitable downside of evolutionary adaptations.[63]

The emphasis on the principle of natural selection to explain disease is perhaps overstated, however. Clearly, in most cases, natural selection will not be the causal factor that doctors will pick up on to explain the occurrence of pathologies among individual patients (but perhaps so at the population level). Counterfactually, though, a charitable interpretation of Darwinian medicine could grant that had the evolution of our species (including our commensal microbes) been different, we may have been less prone to some diseases but perhaps also would have been much more susceptible to others. In that sense, evolutionary biology does account, if only on very general grounds, for why members of our species are vulnerable to disease.

APPLYING EVOLUTIONARY PRINCIPLES IN MEDICINE: AN UNBOUNDED PERSPECTIVE

Another noticeable aspect of Darwinian medicine is that from its perspective, evolutionary biology is relevant virtually to every medically related discipline. In effect, for Nesse and Williams, "there is no branch of medicine that cannot benefit substantially

[63] For a discussion of how to test and apply evolutionary hypotheses in medicine and in biology see Nesse (2011).

from an evolutionary approach in its research and, sometimes, its current clinical practice" (Nesse and Williams 1997, 664). In particular, "evolution provides an otherwise missing paradigm for understanding why our bodies are vulnerable to disease" (Nesse and Stearns 2008, 31), in addition to a "natural framework that "can link diverse aspects of medicine" (Williams and Nesse 1991, 18). Paraphrasing population geneticist Theodosius Dobzhansky (1973), Nesse and Williams have claimed that "nothing in medicine makes sense except in the light of evolution" (Nesse and Williams 1996, 249). I will return to this formulation in the conclusion of this chapter. The book edited by Trevathan et al. (2008) exemplifies the scope of Darwinian medicine's research tradition (despite being titled *Evolutionary Medicine and Health*). Indeed, the introductory chapter announces that an evolutionary perspective is crucial to understanding a number of issues in medicine, such as infectious diseases (including, in this regard, vaccines, viruses, antibiotic resistance, and host-pathogen coevolution), psychological disorders (including depression, anxiety, and mood disorders), nutrition (diets), reproduction (including pregnancy, childbirth, infancy, and childhood), chronic diseases (including cardiovascular diseases), etc. In other words, evolutionary principles are used to investigate whether various biological, behavioural, sexual, and psychological aspects of human life are normal or pathological. From a Darwinian medicine perspective, there are no limits on the extent to which evolutionary explanations can be employed in medicine.

However, it is sometimes unclear in what sense evolutionary principles are explanatory and/or useful. In his *Evolution in Health and Disease*, Stearns asserts that "Human sexual behaviour, reproduction, and the assurance of parenthood are affected by evolutionary forces, often with consequences for the welfare of sons versus daughters. Some of the reasons for the neglect and abuse of children are evolutionary" (Stearns 1999, 6). No one would deny that the abuse of children is a very important and preoccupying social problem with potentially profound consequences for those children's behaviours and psychologies. But it is not clear that child abuse is a medical problem in the same sense that heart disease is. In fact, Stearn's example illustrates that in Darwinian medicine, social, familial, and psychological problems are insufficiently distinguished from genuinely medical ones. Moreover, it illustrates how the methodology of Darwinian medicine is related to that of Evolutionary Psychology.

THE MISMATCH HYPOTHESIS AND BACKWARD LOOKING EXPLANATIONS

Unsurprisingly, for Darwinian medicine's theoreticians, the way in which human beings have evolved is of central concern. This facet is reflected in their support of the mismatch hypothesis.[64] It is significant that some have argued that the most "crucial argument" in Darwinian medicine is that there is a "mismatch" between our genes, inherited from the Pleistocene era, and "present environmental conditions" (Swynghedauw 2004, 134) that causes a number of diseases (Eaton et al. 2002; Nesse 2001, 45). Categories of mismatch range from nutrition to reproductive behaviour (Trevathan et al. 2008). In their first coauthored paper, Williams and Nesse (1991) made a distinction between the environment of evolutionary adaptedness (EEA) (see Bowlby 1969), usually thought of as corresponding to the Pleistocene epoch (1.8 million to 10,000 years ago), to which humans are allegedly "optimally" adapted, and the modern environment, which is "abnormal", even "unnatural", and plagued with the "diseases of civilization", such as diabetes, obesity, cancer, drug addiction, and so on (Williams and Nesse 1991).

The historian of medicine Charles Rosenberg once remarked that early Darwinian explanations of pathologies in the late nineteenth century conceptualized disease from the perspective of "humankind's distant biological past" and attempted to derive "normative lessons about disease prevention and pathogenesis" based on "speculative models of prehistoric biological and social development" (Rosenberg 1998, 338). These remarks can be applied to Darwinian medicine as well. In effect, very much in the manner of Evolutionary Psychologists, Darwinian medicine's theoreticians argue that humans are generally "maladapted" to modern environments and are, in contrast, well adapted to life in Pleistocene-like environments. Indeed, for Williams and Nesse, "human biology is designed for Stone Age conditions" (1991, 1). Both Darwinian medicine's theoreticians and Evolutionary Psychologists appeal to the EEA concept to contrast variations in health

[64] It should be noted that Gluckman et al. (2009) are using a different concept of "mismatch" that brings in epigenetic and other developmental processes. Whereas Gluckman's concept of mismatch concerns individuals who can be mismatched to their environment to various extents, Nesse's concept bears on Homo sapiens. It is the latter concept that is being discussed in this section.

and disease between past and present societies. For example, they argue that "the current epidemics of arteriosclerosis, stroke, hypertension, diabetes, obesity, alcoholism, drug addiction and eating disorders result from the mismatch between our bodies and the environment in which we live now" (Nesse 2001, 45). On this view, the time lag between the evolutionary past of human beings and modern society significantly shapes current states of health and disease among human populations. The argument usually given is that human biology was "optimally" designed by natural selection to meet a number of challenges under environmental conditions that no longer exist. At a more fundamental level, however, this view also seems to suggest that what is "normal" and what is "pathological" ought to be delineated in the light of this distant and somewhat hypothetical biological past. In other words, it is as if the idea of the normal was shaped during the geological era known as the Pleistocene, so that any deviation from this prior evolutionary state ultimately results in disease, pathology, or abnormality. This is at odd with the emphasis Darwin's theory of natural selection places on the idea that biological forms are not fixed but are fluid and changing, and that organisms create new norms of life by adapting to different environments (Canguilhem 1991 [1966]).

The mismatch hypothesis affects how health is understood, how it should be measured, and how such studies should be conducted. Firstly, for Darwinian medicine, the Pleistocene is the gold standard—the environment relative to which health and disease states are to be evaluated. In other words, the Pleistocene epoch operates as a benchmark in understanding common diseases in modern societies. As some have argued, "the most rewarding research [for understanding health differences] involves contrasts between present and previous humans" (Eaton et al. 2002, 115). This is typical of backward looking explanations in the sense that evolutionary principles are applied from the vantage point of the Pleistocene epoch. Secondly, because the paleontological and anthropological records of preagricultural societies are incomplete, contemporary hunter-gatherer populations are used as proxies for understanding the human evolutionary past. "When looking for risk factors for common disease", Nesse and Stearns contend, "the first question is whether the condition is equally common in hunter-gatherer populations" (Nesse and Stearns 2008, 39). Again, Eaton et al. (2002, 113) have argued that "in order to provide an evolutionary foundation for preventive

recommendations [in medicine], the most pressing research need is to identify, contact, interview and examine remaining hunter-gatherers and other traditional people throughout the world".

Although Williams and Nesse do not "advocate a return to any earlier way of life" (1991, 14), it is clear that the proponents of Darwinian medicine account for health and disease variations on the basis of whether individuals comply with regimens, life styles, etc. that prevailed in the social environments of the Stone Age. Cancer research specialist Mel Greaves, for instance, stresses that "the mismatch that increases the risk of breast (and ovarian) cancer falls on women in modern or affluent societies who do not conform to hunter-gatherer lifestyles with respect to reproductive patterns, including breast-feeding" (Greaves 2008, 283). This view, thus, has normative implications regarding what is normal and abnormal beheviour in terms of health, and suggests that a number of diseases result from changes in social and physical environmental conditions broadly construed. One of the challenges this backward looking style of explanation faces, though, is to give empirical content to the EEA concept on which the mismatch argument rests.

There are, however, a number of well-known worries associated with the EEA concept. Firstly, it "discards human evolution" before and after somewhat arbitrary cutoff points (Strassmann and Dunbar 1999, 101), even though human evolution almost certainly began long before and continued on after the Pleistocene era (Downes 2010). From an evolutionary point of view, other transitions, such as to agricultural modes of life, probably played a more crucial role in shaping human health and disease (Strassmann and Dunbar 1999). Interestingly, the evolution of adult tolerance for lactose and resistance to malaria (the latter among heterozygous individuals) are linked to the spread of agriculture and evolved after the end of the EEA, that is, during the last 10,000 years (Ibid.). More importantly, the Pleistocene argument provides a generally inadequate picture of what it means to say that organisms are "adapted" to their environment. In effect, to say that a trait is "adapted" to a particular environment "is simply shorthand to say that the trait was selected over alternative traits in that environment" (Buller 2005, 435). Thus, saying that the EEA is the normal and natural environment of the human species by no means entails that the phenotypes and genotypes of Homo sapiens were

"designed" for or "optimally" adjusted to their Stone Age surroundings. All it can possibly mean is that some variants of particular traits scored higher in terms of fitness than others did in that particular environment. But just as some traits that evolved during the Pleistocene era are now maladaptive, others may be even better adapted today, as amply demonstrated by the reproductive success of the human species.

Finally, to suggest that hunter-gatherer populations were "optimally" adapted to their environment gives the incorrect impression that the Stone Age was a sort of golden age. Anthropologists sometimes (unintentionally) reinforce this perception. For instance, Kiple writes that "early humans were blessed with nutritional plenty and a life relatively untroubled by disease" and that "hunter-gatherers were relatively disease-free" (Kiple 2006, 11–24). While Darwinian medicine's advocates do not hesitate to describe the EEA in empirical terms, they acknowledge at the same time that they "rarely have enough information about past environments and past lifestyles to make a strong assertion about the environment of evolutionary Adaptedness". Yet, they maintain that "such hypotheses are interesting and worth further exploration" (Stearns and Ebert 2001, 427). In light of the conceptual and empirical problems raised by the concept of the EEA one has to be careful in making medical recommendations such as "Stone Age diets", etc., on the basis of the mismatch hypothesis alone (Eaton et al. 2002). However, the main point of the mismatch hypothesis is that bodies are more vulnerable to disease when they exist in environments which differ from those in which they evolved. And this point remains valid despite the series of problems that faces the mismatch concept.

A FORWARD LOOKING VIEW: THE EVOLUTION OF ANTIBIOTIC RESISTANCE

We have seen that a backward mode of disease explanation is a central and somewhat problematic aspect of Darwinian medicine. But whether humans have evolved their physiological features during a particular era is largely irrelevant for a physician in his day-to-day practice. Proximate medicine, so to speak, is usually sufficient for treating disease. Yet, it may be that to successfully treat and/or prevent disease, health professionals will sometimes need to understand *ongoing* evolutionary processes. In this section, I introduce another way of thinking about the role of evolution in medicine by drawing on the notion philosopher of science Paul Griffiths called a "forward looking"

explanation. This approach is underpinned by the idea that what matters for the promotion of health and reduction of disease is not only that organisms are "things that have evolved"—the evolutionary history of which we should reconstruct—but also that they are "things that are evolving" (Griffiths 2009, 14). Unsurprisingly, forward looking explanations are mostly used in the context of the interactions of humans and microorganisms (viruses, bacteria, and so on) that can potentially induce health problems. By focusing on the different and much smaller reproductive timescale of these entities we can see evolution at work.

Consider the recent studies on antibiotic resistance and one of its consequences, the spread of nosocomial (i.e., hospital-acquired) diseases. Because the generation time is much shorter for bacteria than for humans, however, pathogens eventually find ways to circumvent our immunological defences. The evolutionary aspect of antibiotic resistance in bacteria has long been recognized by microbiologists and remains one of the best examples of evolution in "real time". However, the selection of resistance genes in bacterial populations continues to be largely under-appreciated by physicians, as a recent study demonstrates (Antonovics et al. 2007). While antibiotic resistance largely remains unacknowledged as a formal "clinical problem", it nonetheless has begun to be recognized as a "long-term evolutionary issue", notably in intensive care units where it is most problematic (van Saene et al. 2005, 597).

Resistance to drugs means that the efficacy of antibiotic treatments against bacterial infections is decreasing and new treatments have to be developed in order to fight the continually emerging resistant strains that make common diseases more difficult and expensive to treat (Kollef 2006). In effect, from the 1960s until today, bacteria have been developing multiple resistances to a large number of antibiotic classes, including macrolides, methicillin, vancomycyn, and more recently, linezolid (Genereux and Bergstrom 2005). The evolution of drug resistance has many causes, but three main mechanisms are responsible for the augmentation of resistance: (1) the occurrence of mutations on single nucleotides; (2) homologous (or intraspecies) recombination; and (3) heterologous (or interspecies) recombination (Bergstrom and Feldgarden 2008). At the population level, conditions conducive to the development of resistance include the utilization of broad-spectrum antibiotics (i.e., targeting both gram-positive and gram-

negative bacteria), the over-the-counter availability of antibiotics (in many developing countries), unnecessary prescriptions (e.g., for upper-respiratory infections that are often of viral origin), and large-scale agricultural use (Cohen 2000).

The massive use of antibiotics in hospitals, however, is now widely acknowledged as one of the main factors in the evolution of resistance (Goosens et al. 2005). Indeed, the hospital environment creates a formidable selective pressure, which favours the survival and the reproduction of the most resistant bacteria and thereby diminishes the efficacy of the available treatments. For example, the widespread use of b-lactam antibiotics in clinical contexts has prompted the evolution of resistant strains. The response to this selective pressure has been the evolution of b-lactamase enzymes (encoded by the TEM-1 gene) capable of degrading a large number of b-lactam antibiotics and rendering them inactive (Barlow and Hall 2002a).

One of the most direct consequences of this massive use of antibiotics, and consequently the evolution of resistance, is the increasing number of nosocomial diseases (e.g., blood infections, urinary and respiratory tract infections), which pose a threat to patients, especially in intensive-care units (ICU) where they are immunocompromised and acutely ill (Bergstrom, Lo, and Lipstich 2004). As many as 90,000 patients may die of nosocomial infections each year in the U.S. alone (Bergstrom and Feldgarden 2008, 125).[65] Indeed, the presence of resistant bacterial strains that are well adapted to the hospital environment (e.g. methicillin-resistant *Staphylococcus aureus*) stimulates the multiplication of this particular type of infection. But frequently, nosocomial infections result from commensal bacterial flora that become "pathogenic when they multiply in normally sterile sites such as the lower respiratory tract or the blood" (Lipstich, Bergstrom, and Levin 2000, 1938). Hand washing, isolation, and the use of narrow-spectrum antibiotics are among the earliest measures tailored to prevent the spread of infections in hospitals. Recently, more sophisticated methods aimed at counteracting bacterial resistance, based on evolutionary theory and natural selection, have been developed. These include in vitro, or "directed evolution", models (Barlow and Hall

[65] There are a number of difficulties concerning how to measure the ways in which nosocomial diseases affect mortality, morbidity, and costs that I shall put to one side; see Marshall and Marshall (2005).

2002a) and “cycling” and “mixing” antibiotics (Kollef 2006). Whereas the former draw extensively on genetic tools and molecular biology, the latter appeal largely to ecological theory to predict the evolution of resistance. This illustrates the heterogeneity of methodologies and approaches in evolutionary medicine. I outline each of them in turn.

IN VITRO EVOLUTION: MIRRORING NATURE

In vitro evolution is about engineering resistant genes in order to “predict” antibiotic resistance. This technique was precisely developed “for the specific purpose of predicting how resistance genes will evolve in nature” (Barlow and Hall 2002b, 1237). TEM-1 resistant genes, in particular, have been extensively studied because they confer resistance to b-lactam antibiotics such as penicillin, which are widely used in the clinic to treat a large number of infections because of their nontoxicity. In vitro evolution consists in evolving a gene (e.g. TEM-1) in a host (usually *E. coli*) by inducing a number of mutations through a mutagenesis technique. Plasmids are used to express the genes of interest, which are then classified into “libraries” where they are subjected to a number of different antibiotics to see whether resistance mutations will be selected. The *in vitro* evolution method is based on the assumption that evolution in the lab and evolution in nature are analogous processes. This assumption rests on some evidence provided by Barlow and Hall (2002a; 2002b). Their basic idea was to see whether *in vitro* evolution would recover the same mutations as those that occurred in nature. In the case of b-lactams, phylogenetic methods had demonstrated that nine amino acid mutations arose multiple times in response to a set of antibiotics known as extended spectrum cephalosporins (2002a, 829). In their experiment, Barlow and Hall recovered seven of the nine mutations that occurred in nature. This is consistent with other work on protein evolution, which has shown that mutational pathways are evolutionarily constrained (Weinrich et al. 2006). Barlow and Hall concluded that their work provides evidence to support the view that in vitro evolution mimics *in vivo* evolution and that this result allows them to “begin making predictions about the evolution of antibiotic resistance” (2002a, 830).

CYCLING AND MIXING ANTIBIOTICS: ACHIEVING HETEROGENEITY IN HOSPITAL WARDS

During the last two decades, a number of physicians and health care practitioners have investigated the effects of applying different antibiotics in rotation in order to limit the spread of resistant alleles, an approach that is grounded in evolutionary thinking. The underlying assumption of this method is that varying antibiotics over a determinate period of time "can minimize the emergence of resistance because selection pressure for bacteria to develop resistance to a specific antibiotic would be reduced as organisms become exposed to continually varying anti-microbials" (Niederman 1997). Cycling is thus one method of achieving heterogeneity in a given environment. The use of specific antibiotics for a given period of time and then withdrawing and reintroducing them at a later stage prevents bacteria from becoming adapted to their environment. Although some studies have reported significant reductions in resistance (see Kollef (2006) for references), this approach is not without limitations. Clinical microbiologists have pointed out that antibiotic cycling raises a number of methodological issues related to the mechanisms of antibiotic resistance, the dynamics of a particular ICU (e.g. transmission between patients and between patients and medical staff), the composition of the antibiotics, etc., that need to be carefully considered if antibiotic cycling is to be effective (van Saene et al. 2005). This is consistent with recent mathematical modelling suggesting that due to the ecological dynamics of the hospital setting, antibiotic resistance is unlikely to decrease with cycling (Bergstrom, Lo, and Lipstich 2004). In effect, while standardizing antibiotic administration over a period of time increases "long term" heterogeneity in the hospital, it does not increase "local" heterogeneity at the patient level (Bergstrom and Feldarden 2008, 135). These ecological models suggest, however, that "mixing" antibiotics (rather than cycling) holds promise. "Mixing" roughly amounts to administering "all or most available antimicrobial classes" (Kollef 2006, 85) to different patients in order to create a more heterogeneous environment to which bacteria cannot adapt as easily (Bergstrom and Feldgarden 2008, 135). In other words, mixing imposes different selective pressures (at the "local" level) on bacterial strains as compared to cycling. The example of antibiotic resistance shows how evolutionary biology can help us gain a better understanding of a complex medical problem—drug resistance—which is influenced by "ongoing" evolutionary processes. It provides a basis on which to examine

proposed alternatives and to devise future solutions. Moreover, antibiotic resistance explains better why in some cases medicine can hardly do without "forward looking" evolutionary explanations; even a "medical creationist" cannot avoid the consequences of natural selection on resistant strains of bacteria that are continually evolving.

CONCLUDING REMARKS

Following an analysis of the dual reception of Charles Darwin's work by medical doctors during the late nineteenth century (i.e. diseases of evolution and evolution of diseases), this chapter sketched how eugenics concerns have shaped the complex, and often disturbing, relations between medicine and evolutionary biology up to the postwar period, examining how medical advances came to be progressively seen as acting against the Darwinian law of natural selection by allowing "unfit" individuals to live longer and to reproduce. The sole alternative to degeneration found by Francis Galton, Karl Pearson and others to counter the artificial relaxation of natural selection was the promotion of restrictive measures of birth control and selective breeding. This project, politically levered, translated into a harsh social reality in the first half of the twentieth century. While Darwin was not himself a eugenicist thinker, no more than many of his contemporaries at least, his scientific work, and particularly his idea of a constant, gradual improvement of organisms by natural selection in the "struggle for life", provided sufficient room to allow for various and sometimes incompatible social and political interpretations of his theory to be promoted at once. Following the forty-year long "eclipse" of Darwinism in medicine after the Second World War, medical doctors have recently witnessed the flourishing of new evolutionary approaches to health and disease, outside a eugenicist context.

In the second part of this chapter, I have shown that Darwinian medicine and evolutionary medicine are distinct research traditions that emerged from two distinct ways of applying Darwin's theories to medicine, and I have explored several points of contrast between them. First, Darwinian medicine generally applies evolutionary principles from the vantage point of the Pleistocene epoch, while evolutionary medicine studies real time evolution occurring in contemporary environments such as hospital

wards or laboratory settings. Second, whereas Darwinian medicine systematically articulates evolutionary and proximate causes to explain why humans are vulnerable to disease and extends those principles to (social) issues such as child abuse, evolutionary medicine uses the theory of evolution by natural selection to target specific medical problems. Third, evolutionary biology provides a general paradigm to make sense of disease for Darwinian medicine's theoreticians, whilst from an evolutionary medicine perspective, it offers an additional axis of research. Fourth, whereas Darwinian medicine relies extensively on backward looking explanations, evolutionary medicine depends mostly on forward looking explanations. Importantly, in evolutionary medicine, health and disease are not assessed on the basis of a comparison between different lifestyles or different environments, where one is considered "natural" and "normal" and the other aberrant. Fifth, there is a sense in which Darwinian medicine is committed to a particular vision of *Homo sapiens*. This vision shapes the way in which questions about health and disease are investigated and articulated within an evolutionary framework. For example, Darwinian medicine considers humans to be generally maladapted to modern environments but optimally adapted to live in Pleistocene-like environments. Evolutionary medicine, in contrast, is agnostic as to whether humans are maladapted to modern environments. In fact, as pointed out before, just as some traits that evolved during the Pleistocene era are now maladaptive, others may be even better adapted today. Finally, Darwinian medicine is a field of research unified by a set of methodological and epistemological commitments whereas evolutionary medicine is a collection of diverse research programmes working with heterogeneous models.

In spite of these differences, sometimes there is overlap between the two research traditions in terms of the problems they wish to solve or investigate and in terms of individual collaborations, as reflected in recent publications (see Nesse et al. 2010). For instance, antibiotic resistance is recognized by Darwinian medicine as a relevant problem to be tackled from an evolutionary point of view (Nesse 2007). Also, researchers engaged in evolutionary medicine may need to use a form of the backward looking mode of explanation (e.g., to construct microbial phylogenies), although such a style of explanation does not rest on a comparison between past and present human populations. Overall, I would argue that we would gain much by looking at Darwinian medicine and

evolutionary medicine as different research traditions situated on a historical continuum that are both attempting to shed light on medical issues by drawing on Darwinian evolutionary theory. Again, this argument is not intended to create divisions among practitioners but rather to highlight the fact that there are several ways in which the relations between evolutionary biology and medicine can be envisaged.

To finish, let me turn to an aphorism that is often used rhetorically (Nesse and Williams 1996, 259; Gluckman, Beedle, and Hanson 2009, 257) but that, unfortunately, distorts the role of evolutionary biology in medicine. Does nothing in medicine make sense outside the light of evolution? One could imagine that Nesse, Williams, and others were simply making a play on Dobzhansky's words. However, the way they characterize the relationship between evolutionary biology, biological sciences, and medicine reveals the basic role they think evolutionary biology has to perform in medicine. In effect, they assume that "evolutionary biology is, of course, the scientific foundation for all biology, and biology is the foundation for all medicine" (Nesse and Williams 1998, 86). Things may not be so straightforward, however. For instance, although biology and medicine have become increasingly intertwined, medicine continues to be largely an art focused on the individual while evolution looks primarily at the fate of populations. Interestingly, the population approach needed to understand the evolution of resistance illustrates the tension between the individual and population levels because what is good for a patient (i.e. receiving antibiotic treatment) does not line up with what is good for the population (i.e. increase in overall resistance). The ethical and methodological challenge is thus to strike a balance between providing appropriate treatment and "avoiding the unnecessary administration of antibiotics" (Kollef 2006, 82) that increases resistance. Solving this problem would have obvious consequences for medicine and for public health measures more generally. In fact, applying evolutionary concepts and methods to public health might be even more useful than to clinical medicine, because practitioners think precisely in terms of interacting populations, and their evolution.

Finally, what does making sense of something mean? In his article, Dobzhansky (1973) primarily intended to contrast two types of explanations for the diversity of life on earth, namely, the Darwinian theory of evolution with the theories of "special creation" (Griffiths 2009). He argued that only when looking at the diversity of life from the lens of

evolutionary biology can one make sense of the patterns seen in biogeography and comparative anatomy. There is little doubt that evolution can throw some light in various ways on medicine and maybe also on disease patterns. But to say that “nothing in medicine makes sense except in the light of evolution” makes little sense and perhaps no sense at all if we consider medicine to be primarily a practical discipline, that is, “an art at the crossroad of many sciences” (Canguilhem 1991, 35). At any rate, and paraphrasing Wouters (2005), functional medicine without evolution remains incomplete in the sense that it leaves unanswered many questions about disease but not in the sense that no aspect of disease can be understood without invoking evolution.

CHAPTER 3: CONCEPTS IN FLUX AND OPERATIONAL ANALYSIS IN THE LIFE SCIENCES

INTRODUCTION

Philosophers of science have traditionally been concerned with clarifying scientific concepts and stripping them of their ambiguity through logical analysis of language. This was usually done by providing a definition of the scientific concepts. Defining a concept, according to Carl Hempel, is "the most natural and maybe the only adequate method to characterize a scientific concept" (1996, 134 [1966]). Efforts devoted to conceptual clarification were frequently realized by means of logical analyses of language and the production of a *descriptive* or *stipulative* definitions, the former seeking to fix the meaning and the usage of a term; the latter attributing a new signification to a term (Ibid.). During the twentieth century, this concern over the need to define terms unambiguously was often addressed in the context of theoretical reductionism and unity of science to ensure one could reduce the sciences to one another (i.e. reducing the "special sciences" such as biology to another, more fundamental, such as physics).[66]

In contrast, today's philosophers tackling the problem of terminological change argue that clarification is an essential task to pursue in order to ensure fruitful collaborations between distinct scientific communities or research domains. For instance, Potochnik (2011) argues that terminological clarification is crucial for the process of what she calls "sorting out evidential relationships" across different disciplines and fostering genuine collaborative, integrative work in order to grapple with the complexity of the natural world. Potochnik claims that in some cases "differences in terminology can block the way to effective evidence-sharing" (2011, 309), and so hamper collaboration between different fields of science. This argument is echoed by scientists' own avowed desire for precise and standardized nomenclature which they think will facilitate communication among peers and across disciplinary boundaries (see Shaner et al. 1992). Remembering a discussion that took place at the 7th International Conference on Plant Pathogenic Bacteria in Budapest (Hungary) in 1989, Schaner et al. report that during a session, one of

[66] See Nagel (1979); Oppenheim and Putnam (1958).

the molecular biologists was challenged by plant pathologists to apply her studies to the problem of "virulence". In response, the molecular biologist asked what "virulence" was. As a result, she was given three different definitions of the term by well-known plant pathologists. She then asked how she was supposed to go about studying virulence if none of her interlocutors could agree upon what it was (Shaner et al. 1992, 48). This example is by no means an isolated case. If anything, it indicates that precise definitions matter for scientists (not only for philosophers) in order to be able to communicate among themselves and to foster exchange of ideas across disciplinary boundaries, for instance at a meeting.

To take a second example in the same field, another plant pathologist reacted strongly to the suggestion that changes to the concept of virulence and pathogenicity are in order. In his response to his peer's proposition of a terminological change, he replied, referring to Anton de Bary, founder of pythopathology (the study of plant disease) in the late nineenth century:

> I believe, for the sake of effective communication, that we should attempt to stick with the definitions of terms and understanding of concepts that originated deep within our family tree. [...] We should bear in mind the possibility of confusing future generations with terminology rooted on shifting sands. A change in terminology [...] should provide a link between past and future (Hunt 1994, 874).

Now, we should avoid thinking that scientists seeking to maintain tight links with the past of their discipline through terminology are necessarily engaged in some sort of glorification of this past (although this may sometimes be the case). [67] In fact, the remarks of the plant pathologists above are not so odd once placed in context: plant pathologists have debated at length the meaning of the terms pathogenicity and virulence since at

[67] A recent article on virulence and pathogenicity echoed this idea that terminological changes should provide links with the past, stating that "to achieve clarity, it is best to avoid changing concepts in terminology more than necessary. The solution should be based on precedence and unifying concepts within the literature" (Shapiro-Ilan et al. 2005, 1).

least the 1940s and this struggle can explain, in part, the desire to agree to some commonly shared terminology. For example, in the 1970s, The American Phytopathological Society advocated that other such research organizations agree upon the meaning of terms "virulence" and "pathogenicity" as defined by the Commissie voor de Terminologie of the Netherlands Society of Plant Pathology (Thomas and Elkinton 2004, 147). But *terminological* change raises some more important questions about *conceptual* change as well which is, in turn, reflected into, and sometimes guaranteed by, concrete aspects of scientific *practices*.

While I agree with Potochnik that identifying differences and overlaps in meaning is helpful to avoid drawing unjustified inferences, I also think that common terminology is in some cases impossible to achieve and that it can even be heuristically useful *not* to fixate the meaning of concepts too statically– and to maintain it in a state of flux instead – precisely in order to facilitate the cooperative, collaborative work she describes as being a desirable aim for science as a coordinate whole. As I will examine later in this chapter, consensus across scientific communities regarding the meaning of virulence and pathogenicity today is scarce, which does not mean, however, that these concepts are imprecise or lead necessarily to confusion.

In this chapter I examine whether the lack of a common definition of the concepts of virulence and pathogenicity have held back in some way advances and progress in areas such as evolutionary ecology, medicine, invertebrate pathology and plant pathology where the use of these concepts is widespread. More generally, this chapter investigates whether unified, general concepts are necessary to the development of scientific fields, other than to facilitate communication among and between different groups. It asks, on the contrary, if ill-defined concepts be heuristically useful to the growth of knowledge. Combining a Canguilhemian and Rheinbergian perspective on the logic of concepts and practice (chapter 1), and following other philosophers of science (Chang 2009; Feest 2010), I argue that a key aspect of the epistemically productive scientific concepts is their operational potential. More precisely, the claim is that the epistemic value of scientific concepts often is revealed through their being amenable to accommodate a variety of goals in distinct empirical and theoretical contexts which, at first glance, may seem incompatible. In effect, some concepts, particularly in the life sciences, display a curious

polarity and lend themselves to different, almost opposite senses and can be operationalized in either reductionist or more holistic research contexts. Operationalizing concepts provides thus a window into aspects of scientific practices that would otherwise go unnoticed.

Bringing together operationalism and the approach of concepts in flux as recently developed in historical epistemology (broadly construed) may appear inconsistent given that the main goal of operationalism is the disambiguation and clarification of scientific terms by means of operations (e.g. measurement), whereas "concepts in flux" values the productive plurality of meanings attached to the same term over time and across disciplines. However, these approaches can be rightfully combined although such combinaison has never been directly attempted (so far as I know). But it would be missing the point to think that concepts in flux or "fuzzy" concepts cannot be precisely defined. Correctly understood, operationalism or operational analysis is wholly compatible with the view that concepts in flux can have productive effects on science. Bridgman's opeartionalism was criticized because, for him, each new operation presupposes the use of a distinct concept. However, we can view the situation differently, turning it on its head: it is because of the flexibility of concepts that operationalism still has currency and epistemic value. And the task of philosophers of science consists not (only) in finding a more precise definition to concepts but to see how they are operationalized in particular contexts.

I should indicate at the outset that what I have in mind is a more *pragmatic* concept of operationalism and operational analysis than what is usually understood. [68] Here, I will use the concept of "operation" as a guide for a historically-informed, practice-oriented philosophy of science, as recently suggested by Hasok Chang (2009). Focussing on "doings" and "happenings" instead of "objects" and "entities" to use Bridgman's words, I argue that thinking in terms of operation provides a more dynamic perspective on scientific practice. Importantly, my goal is *not* to propose a new philosophy of operationalism but to highlight that operational analysis broadly construed captures

[68] In 1927 Percy Bridgman formulated a new approach to concept called "operationalism" (or operationism).

significant facets of scientific activity and scientific concepts. Paradoxically, a concept having an operational character is what allows it to reach out to other fields, that is, to be "theoretically polyvalent" as Canguilhem (1955 [1977]) once put it, and to contribute in the development and creation of new "epistemic spaces" of research. The general philosophical point here is that we can gain a better understanding of a number of scientific concepts such as virulence using an historical epistemology approach than by any attempts to craft a series of inclusive and exclusive criteria that more or less match the phenomenon we are interested in.

What would an operationalist view of concepts be like in the life sciences? An extreme view of operationalism in the life sciences is that all biological concepts should be defined in terms of actual biological operations, to paraphrase the physicist R. B. Lindsay (1937), an early critic of Bridgman. A more moderate version of operationalism is compatible, though, with the view that the "formation, deformation and rectification" of biological and biomedical concepts, to use Canguilhem's words, is connected to the realm of experimentation and the development of "experimental systems" (Rheinberger 1997). As a consequence, instrumentation and measurement techniques provide a privileged epistemic access to understand concepts "in action".

CONCEPTS IN FLUX

Nowadays, half a century after the demise of logical positivism, and in the wake of the "disunity of science" (Galison and Stump 1996; Dupré 1993), philosophers continue to value clarity and exactitude in science but they have also come to the conclusion that concepts "in flux" (Elkana 1970; Rheinberger and Müller-Wille 2009: Müller-Wille, unpublished), "in tension" (Falk 2000), in addition to "boundary" concepts (Star and Griesemer 1988) and "loose" concepts (Löwy 1992) do not hold back the development of the sciences (or distort communication) but rather make it possible.[69] In the opening of his article on Helmoltz, historian of science Yehuda Elkana illustrated the idea behind the

[69] Already in the 1930s, however, the Polish immunologist and bacteriologist Ludwick Fleck emphasized that concepts have different meaning when used by different "thought collectives". The term "lipid", for instance, has not the same meaning for chemists and immunologists. The variation of meaning attached to terms could, according to Fleck, "lead to scientific innovation" (Fleck 1937, in Löwy 1992, 373).

expression “concepts in flux” with a quote from Hendrik Anthony Kramers (1894-1952), a Dutch physicist who studied with Niels Bohr: “in human thought in general and in the physical sciences in particular the most fruitful concepts are those to which it is impossible to attach a well-defined meaning” (Kramer 1966, quoted by Elkana 1970, 253). According to Ilana Löwy this claim can be extended to the biomedical sciences where, she argued, “fuzzy concepts” that “remain imprecise for their whole life span” [...] can nevertheless “continue to play an important heuristic role in the construction of new knowledge” (1992, 373). The “strength of loose concepts” is manifests, for instance, when it contributes to forge new alliances and relations between distinct social groups. [70]

The labels “concepts in flux” or “boundary objects” capture different perspectives on the nature of concepts and their role(s) in the growth of knowledge. Taken together, however, they suggest that firstly, imprecise concepts can generate productive interplays between the unknown and the known in scientific research; and secondly, that this epistemic role rests upon them having a sort of fluidity or plasticity, both synchronically (they move across disciplinary boundaries) and diachronically (they change over time). If this succinct summary of concepts in flux is correct, then, perhaps the worries expressed by scientists and philosophers at the beginning of the chapter are not completely warranted. In other words, the concept of virulence may be heuristically usefull *because* its meaning is not fixed but fluctuates across disciplines.

This shift from the need to establishing a unified meaning of concepts to the new paradigm of “concepts in flux” was strengthened by the “practical turn” in philosophy, history, and sociology of science instigated by Bruno Latour and Steeve Woolgar’s *Laboratory Life* (1979) by Ian Hacking’s *Representing and Intervening* (1983), and was quickly emulated by others (e.g. Shapin and Schaffer 1985).[71] Famously, Hacking stressed the need to analyse the experimental side of science –which, he claims, has a “life of its own” –, not only ideas or theories, to understand scientific activity. The experimental side of science being closely associated with concrete operations and practices such as

[70] Löwy’s example is the concept of “self” and “non-self” in immunology.

[71] Godfrey-Smith suggested a link between Shapin and Schaffer’s book and Bridgman’s operationalism (2003, 131).

measurements, a renewed version of "operationalism" stands out as a relevant approach to analyse scientific practice further.

The question one needs to ask then is why and how concepts in flux can enhance scientific development. It is obvious that this proposition runs against a very long tradition in philosophy of science starting with logical empiricism but also flies in the face of common scientific understanding. If fluid concepts are not epistemological obstacles to scientific progress in some ways, an important philosophical consequence follows: the well-intended efforts devoted by philosophers of science (and sometime scientists) to clarifying the meaning of concepts (either by providing finer grained definitions or unified, more general accounts) that they perceive were (or are) being handled without sufficient care, precaution and rigor by scientists, can be called into question (Rheinberger 2010b). That is not to say that conceptual clarification is not sometimes much (even badly) needed, but rather that the philosophical problem behind the definitional enterprise has, so far, not really been addressed at its roots and has remained in the background.

To state the problem plainly it may be that the crux of the matter for epistemologists is not so much the realization that clear-cut definitions of concepts are rarely possible (if at all), or even unwanted in some cases, but rather to explain "how and why fuzzy concepts, half-baked definitions, or definitions that overshoot the mark can have positive effects in science" (Rheinberger 2010b, 156).[72] The development of molecular biology provides an illustration of how a complex, immensely successful and fast-developing field of research has been organized and established around a key concept – the gene – whose meaning(s) shifted dramatically throughout the twentieth century and remains, so far, in a state of "productive tension" (Rheinberger and Müller-Wille 2009; Gayon 2007; Beurton, Falk and Rheinberger 2000; Morange 1998). Clearly, because the concept of gene in population genetics and in molecular biology do not overlap does not mean that scientists working in these two disciplines cannot communicate, cooperate and are

[72] For a recent philosophical attempt to introduce new gene concepts following conceptual analysis see Waters (2004).

completely at odds with one another;[73] the deeper issue here is how *despite* this lack of conceptual unification can science develop and progress? The short answer is that this lack of unification, this conceptual polarization, is precisely what makes scientific collaboration and the development of new scientific fields possible.

This aspect of concepts prompts the need for a *historical* epistemology perspective (chapter 1). In addition, this suggests that a good way of analysing scientific concepts is to look at how they change over time following the development of new research methods and techniques, but it also suggests that one should pay attention to the internal architecture of concepts so to speak, which maintains their meaning "in flux" and in doing so, creates polarized tensions that are conducive of scientific development. The above interrogations will lead the development of this chapter on the operational character of concepts in the life sciences, where the discussions and analyses will concentrate on the concept of virulence in particular. The final sections of this chapter will dissect the concept of virulence in more detail, insisting on its internal tensions, and how these allowed this concept to feature in different epistemic contexts, for instance during the bacteriological revolution at the end of the nineteenth century.

THE DYNAMICS OF OPERATIONALISM

Harvard physicist and professor of mathematics Percy Williams Bridgman (1882-1961) encountered operational thinking in the context of understanding Einstein's special relativity theory. According to Einstein, in order to judge that two events separated in space are occurring simultaneously, it is necessary to use a different operation than, say, to evaluate the simultaneity of two events happing in the same place (Chang 2009). The most famous example of operational analysis, however, is of a more day-to-day kind: the concept of "length". Because of our "essential physical limitations" scientists are bound to use different types of measurements for the same concepts in different theoretical contexts, Bridgman claims. When dealing with objects of human size dimensions and moving at a relatively slow speed (with respect to the observer), length can be adequately

[73] Potochnik (2011) considers that according to Dupré (1993), the "incommensurability" of terms (e.g. gene) in several disciplines is such that it leads to the conclusion that science is so disunified that collaboration should be utterly impossible.

measured with rulers, meter sticks and other common measuring devices. However, to measure greater distances such as the distance from the Earth to the Moon, a whole different set of operations is required. To do so one has to infer the distance between the two celestial bodies from calculating the time light needs to go to the moon and come back. As Bridgman said beautifully, "the space of astronomy is not a physical space of meter sticks, but is a space of light waves" (1927, 67, in Chang 2009). The meaning of the concept of length, therefore, changes accordingly with the corresponding methods used to operationalize it.

In his *Logic of Modern Physics* (1927) and elsewhere, Bridgman famously depicted the idea behind operational analysis as follow: "we mean by any concept nothing more than a set of operations; the concept is synonymous with the corresponding set of operations" (1927, 5). Without specific criteria permitting its operationalization a concept is devoid of meaning. While this version of operationalism was widely criticized by philosophers and scientists alike, it remains that operationalising concepts is a central aspect of scientific practice. Developed in the context of the rise of logical positivism and pragmatism, operationalism was unsurprisingly taken up by many as a new "theory" of meaning (Hull 1968), and Brigman's ideas soon became very influential in scientific circles outside physics, especially in psychology and in biology, and were hastily taken up by a number of philosophers of language as well (Chang 2009). Bridgman's ideas underpinning operationalism were not, however, directed to provide a new philosophical theory of meaning as such, but rather to insist on the operational character of concepts in scientific *practice*. Indeed, Bridgman did not attempt to market his approach in terms of a philosophical system or a doctrine; he saw his work as the result of some "reflections of a physicist". As he recalls in 1954, he tried to promote "an attitude or point of view generated by continued application of operational analysis". He said he "abhor the term *operationalism* or *operationism*" because they seemed to imply "a dogma, or at least a thesis of some kind" (1954, 224). The notion of "operationalism", once stripped of its problematic theory of meaning, therefore, holds promises for exploring several aspects of today's scientific practices such as the use of instruments and measurement apparatuses.

THE NATURE OF OPERATIONS

The empiricism that pervades operationalism is intended to test the applicability of scientific concepts to concrete problems. Bridgman's idea that a concept is synonymous with a corresponding set of operations came rapidly under scrutiny. One criticism launched against it was that to follow Bridgman's idea of a concept as being nothing more than a given set of operations will lead one into multiplying concepts *ad infinitum*. For example, it seems to ensue that each measurement yields a different concept of "temperature" (at T_1 … T_2 … and so on). The problem is that according to this principle such measurements cannot be correlated; that is, on Bridgman's account, measuring temperature using different apparatuses boils down to investigating different (ontological) phenomena (see Sober 1984; Chang 2004). This problem is very close to the ones scientists are facing when measuring virulence in a variety of ways while trying to capture a single underlying aspect of nature.

Another aspect of this problem is *what* exactly is captured by the operations. How can we say that what the instruments measure is indeed "temperature", "intelligence", or "virulence"? Hacking once asked, rhetorically, "do measurements measure anything real in nature, or are they chiefly an artefact of the way in which we theorize"? (1983, 233) For instance, psychologists have tried to measure what we call "intelligence" by devising IQ tests (see Feest 2005; 2010 on this). The problem, however, is that even if IQ tests are taken to be the set of operations by which a concept (i.e. intelligence) is measured, there is no guarantee that these tests provide any indication whatsoever into what the pre-theoretical concept of intelligence is (Sober 1984, 71).

As pointed out by Hull, to relate a concept to a set of operations by stating their synonymy is problematic because synonymy is a relation that holds between linguistic entities, not between concepts and operations. Following Hull we can reformulate Bridgman's point as follow: "the meaning of a concept is this set of operations" (1968, 438). Even more precisely, what Bridgman meant is that a concept must be defined "not in terms of properties, but in terms of the operations by which it is made known" (Hearnshaw 1941, 45). To apply it briefly to the example of virulence, one could say that virulence is the result given by the measure of a LD_{50} test or by the variable "α" in the

trade-off model (see chapter 4 and 6).[74] This reformulation of Bridgman's approach places emphasis on the concept of "operations". But what are operations?

Bridgman (1927) distinguished between two broad categories of operations: on the one hand, "instrumental operations" such as types of measurements and uses of observation devices, and on the other, "paper-and-pencil" operations (including mental experiments, verbal operations, logical inference, etc.). Bridgman thought that the former was epistemically superior to the latter which was labelled" symbolic operations" (Hempel 1954, 215). Instrumental operations allow different scientists to perform these operations publicly (giving objective reality to the phenomenon), whereas symbolic operations take place in a person's head, so to speak. In brief, not all operations are public as one would imagine – some are private, in a Wittgensteinian sense. Hasok Chang (2009) noted rightly that this classification lacks precision; what is needed is a more precise taxonomy to distinguish (minimally) simple from complex operations.

At any rate, to operationalize a concept means, in one way or another, to find a way to *measure it* by specifying a procedure to achieve such measures. A straightforward definition of operation could be the following: an operation is an action, involving instruments and reading devices, that allows one to assess whether a concept applies or not, or to what degrees it applies. Analysing operations, in turn, provides a window into the meaning of the concept in use, as well as into the nature of the phenomenon itself. Indeed, scientific instruments and measuring devices play a crucial role in "creating phenomena", as Hacking would say (1983). The term "phenomeno-technique", defined by Bachelard (see chapter 1) refers to this co-productivity between techniques and the object or concept under investigation.

OPERATIONALISM IN BIOLOGY AND MEDICINE

Operationalism was mostly discussed and applied in physics where it originated with the work of Bridgman, and in behavioural psychology during the first half of the twentieth century (Hearnshaw 1941). To some extent these debates are still alive and well (see Feest 2005). Although it is more rarely discussed by commentators, operational analysis

[74] This test refers to the number of deaths above 50% after inoculation.

was also strongly advocated in the life sciences, especially in genetics and systematic (e.g. Stadler 1954; see Hull 1968 for references). This is hardly surprising that operationalism was successful in biology and the life sciences given that a number of central biological concepts (including gene, species, individual, niche, and organism, to name a few, – and as we have seen, virulence –) in biology and medicine are well known for having a fluctuating meaning, both diachronically and synchronically. Moreover, in order to *apply* these concepts one often needs to rely on an operational definition or a set of operational criteria. For example, in the case of the biological species concept (as defined by Mayr) the operational criterion of a group of organisms for being a distinct species is, roughly, the (im)possibility for this population to reproduce (or not) with another, geographically separated population. This illustrates that for operationalism to be successful one needs to provide a way to decide which operations are relevant, and which aren't, when applying a concept. Moreover, as David Hull put it: "In fact, the whole notion of a *set* of operations defining a concept presupposes some way of deciding when the *same* operation is being repeated and when two operations are *different* operations." (in Müller-Wille, unpublished manuscript)

Drawing on Bridgman's work biologists started to criticize biological concepts for *lacking* an operational definition. For example, Paul Ehrlich and R.W. Holm complained that "there are numerous definitions of biological species in the literature, but *none is operational*, since they all include the idea of "potential breeding" and this cannot, by definition, be tested" (1962, in Hull 1968, 448; emphasis added). While this claim admittedly requires further explanation than what can be provided here, the authors later recognized that "like all present-day scientists" their thinking was "influenced by the writings of Bridgman". Although they rejected operationalism as a "philosophy of science" they agreed that "operational definitions are necessary but not sufficient conditions for progress". Yet, if central concepts in biology such as species, niche, and community "are to be useful to biologists", they contended, then "their operational definition is a *sine qua non*" (1963, in Hull 1968, 450). Arguably, it is in genetics – and with the concept of gene – that operational analysis was most fruitfully applied in the life sciences. As Jean Gayon echoed, the meaning of the concept of gene "has dramatically changed over time" and it was given many "operational definitions" in various empirical

contexts (2007, 82). One of the strongest statements in this sense was made by Petter Portin who claimed that "*all* definitions of the gene require operational criteria" (in Rheinberger 2010, 155; emphasis added).

Providing operational criteria for a concept, I suggest, is another way of understanding concepts "in action". Not only the meaning of scientific concepts can be accessed through operational methods but concepts can be used as "tools" in scientific research (Stotz 2009). In other words, giving an operational definition of a number of central scientific concepts is one thing; but the use of concepts *is itself* an operation. Within the operationalist approach the function of concepts in scientific practice ceases to be only about representing the natural world to also engaging with it in a productive way.[75] To recast this point differently, concepts are not about *representation* (alone) but also about *intervention*. Concepts are not innocuous although they may seem so; concepts and their use can have powerful effects both in scientific contexts and in society.

Focussing on the bacteriological "revolution" in the late nineenth century, the next section will outline how and why the concept of virulence was understood in an almost purely operational way, and will draw some philosophical consequences regarding the use of concepts in flux in shaping scientific domains.

REVISITING THE BACTERIOLOGICAL REVOLUTION

The bacteriological "revolution" of the late nineteenth century is often hailed as one of the landmarks of modern medicine. For the late historian of medicine Roy Porter the upbringing of bacteriology as a field is "one of medicine's few true revolutions" (1997, 428) which, according to Charles Rosenberg, "transformed every aspect of medicine" (1987, 141; quoted in Worboys 2007, 21). Indeed, after the formulation of the germ theory of disease by Pasteur, Koch and Lister, public health workers, physicians and epidemiologists were on firmer grounds to assessing the specific, biological causes of

[75] As Uljana Feest recently argued, concepts can be enacted as "research tools" not only in *analysing* data but also in *generating* data. She claims that concepts perform an epistemic function the same way measuring instruments do (2010, 181).

infectious diseases such as anthrax, cholera, tuberculosis, and many others. In the context of "laboratory medicine" which proceeded to a redefinition of disease identity by shifting the focus to their (microscopic) cause (Cunningham 1992), the (so-called) Koch's postulates provided a way to identify specific, necessary (and not only sufficient) determinants of disease (Carter 1985).[76] As a consequence of this one-organism, one-disease model, bacteriology also operated a redefinition of the concept of a healthy organism as one free from those putative pathogenic germs (Gradman 2001).

Parenthetically, the adoption of this epistemological position by the European founders of medical bacteriology marks the beginning of the exogenous style (chapter 5) in which the virulence of a disease is correlated to an organism's structures or functions in virtue of which it is said to be pathogenic (or virulent). The belief that pathogens form a distinct class of organisms which can be identified by laboratory techniques such as Koch's postulates led the way into the development of the molecular style of thinking about virulence and infection. On this view, pathogenic mircoorganimes possess structural or functional properties which place them within a particular class of living things. In contrast, the exogenous (or ecological) style (chapter 4), also growing out of medical bacteriology, blurs this distinction by insisting that parasistism (of which infectious diseases are one example) is a relative category that reflects either a lack of adaptation beween two species or, in contrasts, a successful adaptation on the part of the pathogen to its ecological niche. The line between pathogenic and non-pathogenic organisms, however, is one that cannot be drawn once and for all because the nature of the association between two different species changes depending on the environment.

To come back, the germ theory of disease had deep political and social consequences in how best to handle the waxing and waning of epidemics and to limit the spread of infectious diseases among populations.[77] Recently, however, the idea of a unified "germ

[76] The Koch's postulates can be summarized as follow: 1) a specific microorganism must always be found in the diseased tissue, cell, or organ; 2) this specific microorganism must be cultivable in pure culture; 3) the pure culture, when inoculated to a healthy organism, must cause the disease specifically; 4) the same disease-causing microorganism can be recover from the inoculated organism (see Carter 1985; Worboys 2007). See chapter 5.

[77] How best to prevent the formation of epidemics remained a thorny issue on which "contagionists" and "infectionists" were long divided (Gaudillères and Löwy 2001, 1).

theory" of disease was challenged: it was argued that there was no such thing as a bacteriological revolution in the late nineteenth century. The concept of "revolution", in the sense of Thomas Kuhn (1962) began to be used by professional historians in the 1970s although it does not reflect the complexity of the situation, not just in England (Worboys 2000) but admittedly in the rest of Europe as well (Worboys 2007). What Worboys argues, examining four paradigmatic diseases at the end of nineteenth century, is that the decade of 1880 *was not* characterized by radical shifts in preventive measures derived from laboratory knowledge as the term "bacteriological revolution" suggests. Instead, this so-called "bacteriological revolution" is imbued with conceptual and practical continuities and spans a longer time period, that is, from 1870 until 1910.

But others have revised the usual historiography of bacteriology on still another count. Bringing to the fore the (largely neglected) role of experimentation, control measures and manipulation in bacteriology, Andrew Mendelsohn (2002; 2005) provided an original interpretation, with far-reaching philosophical consequences, of the period circa 1880-1930. If Mendelsohn is right, the development of bacteriology both in France and in Germany was not based on the development of a unifying germ theory of disease – often seen as forming the theoretical core of this transformation – but rather on an "old concept given new meaning: virulence", loosely understood as the capacity for a pathogen to cause disease in a host (2002, 4). Mendelsohn argued that during the last two decades of the nineteenth century the concept of virulence was an "intellectually empty, almost *purely operational concept*" in the sense that "virulent cultures killed, attenuated ones did not" (2002, 5; emphasis added). This dichotomy between virulent and avirulent cultures was conceived as the result of *within* species biological variations – a concept that was then recently problematised by Darwin in *On the Origin of Species* (1859).[78]

[78] I stress "within" species because Pasteur did not believe that microorganisms could transform into one another at will. Circa 1880, however, bacteriologists and most famously Nägeli, advocated the doctrine of pleomorphy which stated that a same organism could exist under different form. "Bacteria are inconstant and continually lose themselves in one another" (Nägeli 1879, in Farley 1974, 145). As a consequence of this doctrine the concept of species was difficult to apply to microorganisms. The development and application of the technique of "pure culture" by Robert Koch was one of the ways bacteriologists found to control variation among microorganisms (Gradmann 2001).

The laboratory context of the Pasteur Institute provided an ideally controlled environment to study variation in virulence in experimental animals which were inoculate with bacterial strains. After serial passages of the strains in these laboratory animals (the order was usually rabbits, sheep and guinea pigs) experimenters could observe either an increase or a decrease in the level of virulence of the original strain. The attenuated effect of a strain, however, could be limited to one or two organisms, and more puzzling still, the strain could in some cases often revert to its original virulence. Such returns were interpreted by some in broad, evolutionarily terms (see chapter 4).

Towards the end of the nineteenth century "there was no standard unit of measure, no 'meter' or 'ohm' of virulence", however (Mendelsohn 2005, 87). Although methods of attenuation varied a great deal among bacteriologists, and despite the lack of a common standard unit of measure for virulence "the anthrax vaccine […] *was* uniform" (Mendelsohn 2005, 87; emphasis in original). Laboratory induced modifications of virulence were considered lasting and heritable (although some could revert to the original type) as they were conserved in the final product: the vaccine. Using host's death and other observable signs, scientists were able to distinguish between virulent and avirulent cultures well enough –had they been incapable of doing so, the production of vaccines would have been utterly impossible. The development, production and use of vaccines, in effect, rested to a large extent on technical means, laboratory procedures and institutional structures (i.e. Institut Pasteur) that allowed to firstly, attenuate the virulence of a given strain by serial passages; and secondly, to guarantee that the attenuated organism (i.e., its level of virulence) will remain constant. [79] The history of Koch's tuberculin is a case in point (see Gradmann 2004).[80] In the middle of the twentieth century, many continued to acknowledge that "[virus] virulence is almost indefinable and practically impossible to measure". These were the exact words of Stuart-Harris in the

[79] Scientists also had to ensure that when the vaccine will react within the host's system it will not trigger a virulent reaction from the immune system.

[80] Koch identified tuberculosis bacillus in 1882, establishing his reputation worldwide. Ten years later, he announced the discovery of a cure to tuberculosis in summer 1890, which was quickly followed in November by the release of the substance able to yield this effect, i.e. tuberculin. This success story was short-lived, however, and patients inoculated with the medicine started feeling ill and a number of them died. By today's standards, "tuberculin can cause death in a few hours" (Gradmann 2004, 474).

opening talk of a Ciba symposium on Virus, Virulence and Pathogenicity held in London (1960, 3). Nevertheless Stuart-Harris pointed out in his concluding remarks that there are *practical* reasons for thinking about how virulence can be defined and measured, chief among which is the possibility of creating attenuated vaccines, for instance to cure polio (1960, 12).

To sum up, at the Pasteur Institute researchers like Roux, Chamberland, Pasteur and others conducted experiments on infectious diseases with guinea pigs and other model organisms, investigating the changing nature of virulence. Changes in bacterial cultures were controlled and induced artificially by serial passages through animals but this variation could also be controlled and manipulated in these systems to the extent that large-scale production and distribution of vaccines, within and outside France, became possible (see Mendelsohn 2005).[81] Although virulence is perhaps the "theoretically emptiest of key concepts" in the life sciences and was recently ranked as "the least defined and remembered element of early bacteriology" (Mendelsohn 2002, 6-17), this concept "was the hub of a theory". In effect, "upon it turned a whole structure of etiological, epidemiological, and biological explanation" (Ibid. 18). In other words, despite its lack of theoretical underpinning (or perhaps *because* of it) the concept of a "variable virulence" became the "signature of disease explanation at the Institut Pasteur" (2002, 9).

Indeed, Pasteur reported that by successive passages through an animal "new virulences and new contagions can be created". Moreover, variations of virulence could "explain how certain great epidemics [typhus] have appeared at one time or another" and how "smallpox, syphilis, plague, yellow fever appeared across the ages" (Pasteur, Chamberland, Roux 1881, 435, quoted in Grmek 1995, 270). As it turned out, the concept of virulence (although ill-defined) offered a dynamic, flexible explanatory framework to account for the origins of disease germs and disease causation, not merely in (reductionist) terms of germs as invading agents, but as the consequence of ongoing (evolutionary but Lamarckian) interactions between host, pathogens and changing environmental conditions (Moulin 1992).

[81] A similar argument could be made in the case of Koch (see Gradmann 2001).

THE ROLE OF CONCEPTS IN SHAPING THE LIFE SCIENCES

If Mendelsohn's account is sound, it strengthens two important philosophical theses. Firstly, that science does not necessarily develop by formulating abstract *theories* to be later put to test by precise experiments (as Popper would, roughly, have it) but by reformulating old *concepts*; and secondly, that operational concepts can also have a positive effect on the development of science. Let us start with the first one.

Philosopher Karl Hempel famously defended the idea that scientific disciplines emerge thanks to the formulation of abstract laws of nature. In his paper on "The theoretician's dilemma" (1958), for instance, he claimed that

> the early stages in the development of a scientific discipline usually belong to the former level, which is characterized by the search for laws (of universal or statistical form) which establish connections among the directly observable aspects of the subject matter under study (1958, 41).

From the previous discussion it is plain that bacteriologists at the Pasteur Institute did not try to "test" the so-called germ theory of disease by experimenting with changes in virulence; the experimental practices developed around the problem of controlling and understanding variation in virulence did not rest on there being a body of theory (or not) to explain these variations in degrees of infectiousness. Nor were they trying to formulate general laws about the behaviour of microorganisms in infectious diseases. The formation of the bacteriological paradigm was not organized around a well-defined body of theoretical knowledge but rather on a loosely defined concept: virulence. In *Logic of Life* (1970) the Nobel Prize laureate in Physiology and Medicine François Jacob emphasized that the development of the life sciences is more often than not organized around the formation of *concepts* rather than *theories* (Rheinberger 2010, 45).

However, this does not mean that theories (or theoretical terms) had no role to play in the organisation of research in this field; what it means is that, more broadly, in the life sciences, experiments and theories are so "intricately interwoven that the function of experiments as an instance of testing hypotheses appears to be largely marginal" (Hagner

and Rheinberger 1998, 363). [82] This last point appears to be precisely what Mendelsohn has in mind when he suggests that a whole field of research like bacteriology was organized around a single "ill-defined" concept that is being operationalized in various ways by distinctive methods, skills and laboratory procedures (2002, 18). The bottom line here is that bacteriology emerged as distinctive and coherent scientific field of research by constructing what is now called "experimental systems" (Rheinberger 1997). According to Rheinberger, an experimental system is the "smallest functional unit of research" that enables researchers to perform a set of operations in order to investigate (and partly, create) specific phenomena. An experimental system consists of instruments, scientific apparatuses, measurement techniques, experimental organisms which become research tools in this context, control procedures, and so on. Such concatenation of technical, conceptual and other means allows for controlling and decomposing the ontological complexity of the phenomena studied (the "epistemic thing"), while at the same time retaining its complexity, epistemically so to speak, through the features of the experimental system (Rheinberger 1997).[83]

Another central aspect of an experimental system is that "it helps us to understand how new knowledge – that is knowledge that in essence cannot be anticipated – is generated in the process of research" (Rheinberger 2011, 13). This feature of experimental systems relates to the idea that concepts can be in a state of flux, characterized by undefined meaning, and still be in a position to drive science further into open-ended research avenues. In sum, the growth of science (at least the life sciences) and its applications are not contingent upon developing abstract, general theories, or fully coherent theoretical concepts but rather on the construction of historically-localized, practice-embedded "systems" and "concepts" which provide control over the

[82] At that time, in the context of the Pasteur Institute, there was at least one other theory seeking to explain inflammation and response to infection: the phagocytocis theory of Ely Metchnikoff. A full historical account of the connections between immunology and bacteriology is still lacking but see Mazumdar (1995).

[83] The engineering and use of "model organisms" in the life sciences is the typical example of how reducing complexity (i.e. investigating smaller-scale organism under experimentally-controlled conditions) can yield general knowledge by providing insights into the function, evolution and development of a whole range of so-called "higher organisms" (see Ankeny and Leonelli 2011).

phenomenon under study. Hence this is why a careful attention to the materiality of science and scientific practices is crucial for historical and philosophical reconstruction of particular episodes across shorter or longer time periods.

DRIVING SCIENCE FORWARD

The second philosophical thesis supported by Mendelsohn's reading of the bacteriological "revolution" is that theoretical concepts are not (always) the main drivers in moving science forward: *operational* concepts too can have a positive impact on the development of particular fields of inquiry – in virtue of them not having a precisely fixed meaning, but rather by being in a state of productive tension.

The distinction advanced here between "theoretical" and "operational" concepts may seem artificial and can recall a naïve version of instrumentalism, so let me clarify it briefly. Jean Gayon remarked that philosophers "distinguish observational and theoretical terms in scientific theories" (2007, 81; Nagel 1979; Hempel 1958). Whereas the meaning of observational terms (e.g. "temperature"; "pressure") is fixed by observational, empirical procedures, the meaning of a theoretical term like gene changed over time and was constantly redefined in many different "operational ways" (2007, 81). Other like Bridgman emphasised that some theoretical concepts have only indirect links with operational procedures (e.g. wave function in quantum mechanics or strain and stress inside a solid body) at all and were, as such, "not amenable to direct operationalizations" (Chang 2009). David Hull, for example, asks how evolutionary biologists operationalize "theoretical terms" like fitness (1999, 489), while Elliott Sober emphasized that "theoretical claims ought to be testable – i.e., rendered 'operational'" (1984, 82). It would seem, thus, that both observational and theoretical terms can be defined by a set of operational criteria. Regarding the example discussed here, virulence was (according to Mendelsohn) however "almost a purely operational concept", i.e. nearly wholly devoid of theoretical content. While virulence in the work of Pasteur was almost entirely observational, it acquired some theoretical content following its inscription into a mathematical equation (see chapter 4) and following its operationalisation through concepts like "virulence gene" or "pagthogenicity islands".

I will thus, for the moment, oppose theoretical and operational concepts, bearing in mind that theoretical concepts also have to be operationalized in various empirical contexts. There is another reason to hold on to this opposition: philosophers not only argued that theoretical terms are less operational than others but that it is in virtue of this that can they accomplish their "systematizing function" in science (see Hempel 1958; Hull 1968, 438). The fact that theoretical terms cannot (always) be operationalized is even seen as "essential", it is claimed, if "scientific theories are able of growth" (Hull 1968). Indeed, one strong criticism of Brigman's operationalism is that operational concepts are not the ones driving science forward; this role, on the contrary, is played by theoretical concepts: "theoretical terms [...] are not completely operational, but they are *necessary for the progress of science* (Hull 1968, 455; emphasis added). To use the words of the systematists Michler and Donoghue, rephrasing Hull's point: "a concept cannot be completely operational and still be useful for the growth of science" (1982, 494). In brief, there is a strong assumption among philosophers of science that theoretical concepts (in contrast to operational ones) are essential to the development of scientific knowledge. Underneath this assumption is the older idea that theoria is prior to praxis. However, in the history bacteriology one finds the opposite (Mendelsohn 2002; Moulin 1992).

Traditionally, the value of operational concepts and operational analysis was downplayed by philosophers of science. Indeed, influential thinkers including Poper, Hempel, (1954), Hull (1968), and Sober (1994; 1984) have openly criticized operationalism on a number of counts (for a review, see Chang 2009; Feest 2010). In his (1968) Hull was very sceptical regarding the real value of operational analysis, for both science and philosophy. Indeed, even if he agreed that operational analysis could sometimes yield interesting perspectives, he thought a great deal of it was plain "non-sense". As he put it in the case of genetics:

> The fate of the various operationally defined units in genetics [muton, cistron, etc.] has been either to depart from their original operational definitions and become theoretical entities or to retain their operational character and decrease in importance (1968, 446).

David Hull has a curious love/hate relationship with operationalism that was not picked up by commentators (see special issue in 2000 in *Biology and Philosophy*). In his *Science as a Process*, Hull stated that Bridgman created "a Frankenstein monster that had gotten away from him" (1988, 126). In his (1968) he offered a robust attack on operationalism in physics, biology (especially in systematic and genetics) and psychology. Thirty years later, however, he stated that if his colleagues could move on with traditional philosophical issues such as the Twin Earth problem and incommensurability "they would find this topic [operationalism] rewarding" (1999, 489). Moreover, Hull argued that it is an essential task for philosophers to understand how to operationalize concepts in science as well as in philosophy (Hull 1998). [84] Indeed, in an insightful comment Hull pointed out the relevance of taking an operationalist perspective in order to gain a better understanding of science as a *set of practices* (not his expression). In a paper on Popper's philosophical legacy Hull observed that one of the problems in operationalising concepts is that "very little has been said by philosophers of science or scientists for that matter about how to operationalize concepts" (1999, 489). He agreed that, on the one hand, as a theory of meaning operationalism is "bankrupt" but, on the other, "we have said precious little about how concepts are to be operationalized". Part of the reason for why this is, according to Hull, is that focussing on operations will lead philosophers to think in a very different way than what they are used to. In effect, it leads them to analyze historically and temporarily localized practices and knowledge production. As Hull says, operationalism "seems highly contingent and particularized, the very sort of phenomena that we philosophers shy away from" (1999, 489). Obviously, looking at localized, historical knowledge and practices goes against the long-held idea of scientific knowledge as being concerned with finding general, abstract laws of nature through the means of a (a)temporal scientific method. In a far-reaching remark he pointed out that "scientists themselves just *do* it, they operationalize their concepts without saying much *how* they do". Recognizing this situation as one needing an explanation, Hull urged philosophers of

[84] "Empirical investigation requires the operationalizing of the concepts we are attempting to apply. Philosophers have contributed to our understanding of science by showing that theoretical terms cannot be operationally defined in a literal sense of 'definition', but this impossibility proof is not enough. We still need some discussion of how to operationalize our concepts" (Hull 1998, 211).

science to look into "how" scientists actually develop ways of operationalising concepts over time and in different empirical contexts.

As we will become clear in the next sections, despite several attempts by scientists to provide clearer definitions, the concept of virulence remains very much operational. It is, however, "intellectually empty", to use Mendelsohn's expression, only if one believes that scientific concepts must be defined in an unequivocal an unambiguous way in order to provide a handle on nature, and/or to contribute to the growth of science. I should indicate, again, that the main point of this chapter is neither to provide a full defence of operationalism nor to argue that every concept ought to be operationally defined in order to be meaningful, or simply useful. I do not want to erase clarity and precision from the list of scientific (and philosophic) epistemic values. More down-to-earth, my contention is rather that for a concept to have what Mendelsohn called "an almost purely operational meaning" is not necessarily unfortunate, at least from a philosophical point of view.

THE CONCEPT OF VIRULENCE

The concept of virulence is old and comes from a very distant past. For centuries, it designated at once chemical reactions occurring inside organisms and the parasitism of one species by another (Arloing 1891). Nineteenth century *Littré* dictionary (online) states that virulence derives from the latin "virulentia" which means "poison" (Casadevall and Pirofski 2001). In *The Bacterial Cell* microbiologist René Dubos devoted an entire chapter to discussing the nature of virulence, which he characterized as an "immensely complex property, the summation of many complementary attributes" (1945, 228). Dubos noted that the concept of virulence was used before the formulation of the germ theory of infectious diseases to designate "the poisonous quality of an agent" or the "severity of a disease or of an epidemic" (Dubos 1945, 188). Dubos knew, however, that virulence could not be explained (only) in terms of a property of the invading microorganism. Following the American bacteriologist Theobald Smith he argued that in order to understand the nature of virulence, the properties of the invaders are not sufficient; the biology of the invaded host had to be taken into account as well (1945, 189; Smith 1934). As he would put it in a later work, virulence is an "abstract concept" that refers to the relation between host and pathogen (1959, 78). At the beginning of his career Dubos worked with

Oswald Avery at the Rockefeller Institute on the changes in virulence in pneumococcus culture and was also aware that virulence was related to a material support in the cell (chapter 5). He acknowledged, however, that cellular, organismal and ecological contexts had to be carefully considered (chapter 5).

Nowadays, any microbiologist asking "what is a pathogen and what is meant by virulence will meet with derision at best and will probably be declared a heretic bereft of his sense" (Isenberg 1988, 40). As microbiologist Isenberg pointed out, for most people, harbouring doubts about "the meaning of pathogenicity and virulence seems inappropriate, if not ridiculous" (Ibid.). And yet, the meaning of the concept of virulence is still debated (Poulin and Combes 1998; Read 1994), although the concept continues to be applied widely. Reviewing the multiple definitions of the concept of virulence microbiologists Casadevall and Pirofski (1999) suggested looking at the history of this concept through the changing perspectives of the "pathogen-centred view" and the "host-centred view". According to the authors, early definitions of virulence in the twentieth century were "pathogen centred", i.e., they were "based on the assumption that these characteristics [virulence and pathogenicity] were intrinsic properties of microorganisms" (1999). Virulence, they claim, was conceptualized as being a particular property of the pathogens, unrelated to hosts' defence mechanisms or immune system. The pathogen-centred view of virulence predominated during the late nineteenth and early twentieth century, Casadeval and Pirofski contend, because of the emergence of numerous diseases due to "toxigenic" bacteria (e.g. diphtheria), against which the immune system was almost always deficient, and because of the strong emphasis the germ theory placed on the causative power of microorganisms in producing disease (1999, 3703-4).

However, this reconstruction is partly a historical artefact. Indeed, microbiologists became very early on aware of the fact that virulence is not "absolute" but "relative" (to the host) and that it results from "the conflict between two living beings", namely the host and the pathogen. A number of factors including the age, the nature and overall, the "individuality" of the whole animal in which virulence is expressed have to be considered, as Emile Duclaux pointed out (1896, 379). Similarly, Dickinson, an English physician, concluded his article in *Lancet* on "The seed and the soil" (1902) by stating that most

interactions between living things "can be looked at from two points of view – the donor and the recipient, the attacking and the attacked, the seed and the soil". However, he continues "one who desires to see the whole of what is before him must have regard to both" 1902, 1301). These were not attempts to promulgate an indistinct form of holism in biology but rather expressed the conviction that virulence result from an interaction between living systems.

Recently, discussions about the concept of virulence have been conducted from various perspectives, including empirical and theoretical ones (Combes 1998). The "received view", so to speak, defines virulence as "the ability of a pathogen to multiply and cause harm to its host" (Calow 1998 in Combes and Poulin 1999, 474).[85] However, the concept of virulence raises further definitional issues in several fields, including medicine, plant pathology, evolutionary biology, pathology, and microbiology (Shapiro-Ilan et al. 2005). In their review (1999) already mentioned Casadevall and Pirofsky observed that virulence could be define according to many criteria such as the degree of pathogenicity; the strength of pathogenic activity; the relative capacity of pathogens to overcome available defences; as disease severity assessed by a reduction in host fitness following infection or as percent of death per infection. Virulence can also be understood as a synonym for pathogenicity; as a property of invasive power of microorganism; as a measure of the capacity of a microorganism to infect or cause damage to a host or as the relative capacity to enter and multiply in a given host. Finally, the authors suggested defining virulence as "the capacity of a microbe to cause damage in a host" (1999, 3704).

This multiplicity of meanings is perhaps not so surprising because the concept of virulence is invoked in the explanation of pathogen's mode of transmission; the adaptive dynamics of host-pathogen interactions (within-host and inter-host); in the evolutionary models of virulence (kin-selectionist, multilevel-selectionist, nested models, and multiple infections model, and so on) as well as in infectious diseases management by public health services, medicine, veterinary and agriculturalists (see Dickmann et al. 2002 for overview). In fact, it could be stated with bacteriologists working in the 1930s that "the

[85] It should be noted that the concept of "harm" remains vague (like in political theory) and is still in search of an appropriate characterization and operationalization.

problem of virulence has been and still is among the most arresting and fundamental subjects in the study of infectious diseases" (Arkwright 1929, 5541). In spite (or perhaps because) of the centrality of the concept of virulence in the field of infectious diseases, medicine and evolutionary ecology there is no generally accepted definition of virulence yet (Ebert and Bull 2003; Gandon et al. 2002; Poulin and Combes 1999). As British bacteriologist W.W.C. Topley has put it nearly one hundred years ago, virulence remains "an elusive term" (1919, 4).

VIRULENCE AND PATHOGENICITY

One conceptual difficulty in defining and measuring virulence is that it can easily be conflated with closely related concepts such as "pathogenicity", "infectivity" and "toxicity" (Stuart-Harris 1960). The persistency of this situation is confirmed by the several papers published during the 1920s, 1930s and 1940s (Ball 1943; Dudley 1924; Arkwright 1929; Topley 1941-42; 1919a,b,c; Thiele and Embelton 1913) attempting to clarify and detangle these issues by providing more clear-cut definitions of the terms involved. How to discriminate virulence, infectivity and pathogenicity is still matter of debate nowadays (Ulvestad 2007). At any rate, biologists seem to suggest that virulence comprises two main features: "invasiveness", i.e. "the ability of the organism to establish itself and propagate in the host tissues" and "toxicity", i.e. "the ability of the organism to destroy or damage tissues or impair their physiological functions" (Hawker and Linton 1979, 310). Later on this distinction was made on the basis of the concepts of "'infectivity' (i.e. the ability to colonize and invade a host) and 'severity' of the disease that is produced" (David et al. 1990, in Read 1994). Along the same lines, Kirchner and Roy (2002) have recently argued that a pathogen's virulence has two components: "infectiousness", meaning roughly the "aggressiveness" of a pathogen in transmitting itself from one host to another; and "lethality", namely the "severity" of the pathogen's "impact on its host' lifespan" (2002, 28).

What these different definitions indicate is that virulence can still be "viewed as a property of the pathogen, or as a property of the host-parasite interaction (and thus as much a consequence of host resistance as of any parasite traits" (Read 1994, 73). In effect, the first part of each of the definitions given just above designate the ability of a

pathogen to infect a host and transmit itself to other hosts whilst the second part indicate the degree of harm or disease caused to the host following its interaction with a pathogen. The dualism resulting from the preceding analysis confirms that virulence is "a relative term" (Hawker and Linton 1979, 310). This dualism overlaps with the definition of virulence and pathogencity, the former being described in qualitative terms, and the later, formulated in quantitative terms, expresses the power of a pathogen to invade a host's defence system. One may ask, however, why virulence and pathogenicity are so often conflated, identified or sharply separated. To understand this point it is worth going back to the article of British virologist Stuart-Harris mentioned above. In this article he supported Miles (1955) who distinguished virulence and pathogenicity as follow: pathogenicity should be regarded as "an attribute of a species, genus" or other grouping and reserving the use of virulence for the "expression" of pathogenicity (Stuart-Harris 1960, 3). In other words, pathogenicity is the "power" to produce pathological effects in a host whereas virulence is the "evidence" of such power as measured by the observation of signs, symptoms, and degree of illnesses or host-death (Ibid. 3-4). The distinction between the power of a microorganism to cause harm (pathogenicity) and the degree of harm that is being caused (virulence) was recently revived and debated again (Shapiro-Ilan et al. 2005; Thomas and Elkinton 2004). The distinction proposed by many is that pathogenicity is an all-or-nothing feature (i.e. a pathogen is pathogenic or it is not); whereas virulence comes by degree. The following table (from Shapiro-Ilan et al. 2005) reflects this distinction.

Table 1. Concepts of pathogenicity and virulence (adapted from Shapiro-Ilan et al. 2005)

Reference	**Pathogenicity**	**Virulence**
Steinhaus and Martigoni (1970)	The quality or state of being pathogenic. The potential ability to produce disease	The disease producing power of an organism. Degree of pathogenicity within a group or species
Aizawa (1971)	... the ability of a strain or species of micro-organism to produce disease in various hosts (term is used qualitatively)	Degree of pathogenicity against a specific species host in controlled conditions within a group or species of microorganisms (term used quantitatively)
Cantwell (1974)	The quality of being pathogenic	The quality of being virulent; the quality of being poisonous; the disease producing power of a microorganism
Tanada and Fuxa (1987)	The ability to invade and injure the host's tissues. Applies to groups or species of pathogens	The disease producing power of the pathogen, the ability to invade and injure the host's tissues. The degree of pathogenicity within a group or a species
Tanada and Kaya (1993)	Nearly synonymous with virulence but applied to groups or species	The disease producing power of a microorganism. The ability of a microorganism to invade and cause injury to the host. The relative capacity of a microorganism to overcome the host defence mechanism... The degree of pathogenicity with the group or species
Lacey and Brooks (1997)	The quality or state of being pathogenic. The potential ability to produce disease. Applied to groups or species	The disease producing power of an organism. Degree of pathogenicity within a group or species
Thomas and Elkinton (2004)	The number of dead individuals relative to the number exposed to the pathogen	The number of dead individuals relative to the number of infected

Table 1 show that the terms virulence and pathogenicity can be distinguished analytically, although in practice they often tend to overlap or to be used as synonymous. The confusion of these terms denounced by many, moreover, is only apparent. In effect, although the concept of virulence is in flux its meaning can be fixed through the use of concrete measurements. In other words, it can be made clear on a case-by-case basis when the operations in measuring virulence (or pathogenicity) are specified. As Shapiro-Ilan et al (2005) noted "operational definitions are useful in identifying empirical

approaches to determine whether an organism fits the criteria of pathogenicity and virulence" (2005, 3). The next section will illustrate how the division of labour among scientific field also plays a part in creating the impression that virulence is a confused or confusing concept. When the context in which the term is used is stated clearly, confusion regarding its meaning hardly occurs. In brief, on can have both a concept that remains "in flux" without having to give up precision in its meaning. This dual characterisation has, however, a broader historical and philosophical meaning. It gestures towards the two styles of reasoning I presented in the introduction. Virulence can either refer to the host-pathogen's relation in a given ecological environment, or it can refer to various properties of the pathogen, such as the capacity to breach a host's cellular defences (pathogenicity). One could say that there is an ecological and a functional conception of virulence at play here.

DIVISIONS OF LABOUR AND THE PROBLEM OF MEASUREMENT

The epistemological importance of the act of measuring in science was perhaps only recognized in the mid, even late nineteenth century (Kuhn 1977b). As Lord Kelvin once suggested, "when you can measure what you are speaking about, you know something about it; when you cannot measure it [...] your knowledge is of a meagre and unsatisfactory kind" (Kelvin 1889 in Hacking 1983, 242). Kelvin's comment directly applies to the problem of virulence addressed in this chapter. In fact, measurement is sometimes not only the best, but the only way of gaining insight into the nature of a phenomenon. For instance, because it is no material object as traditionally conceived, virulence can only by understood satisfactorily by measuring, comparing, scaling or ranking different levels of virulence against a previously established standard. In response to Thomas and Elkinton (2004) who stated that useful definitions of terms like pathogenicity and virulence must be conducive of explicit ways of measuring them, Shapiro-Ilan et al (2005) argued that "there is no requirement that a scientific term be quantitatively measurable in order to be useful" (2005, 4).

In this section I argue that the distinction between pathogenicity and virulence described above is neither the result of historical necessity nor ontological reality; it reflects to a large extent a division of labour among scientists and how each scientific field

chooses its own way of measuring and comparing the phenomena they study. As pointed out already the choice of one definition over another is discipline-dependent and varies according to the goal(s) of the field, the research questions and the methods employed to inquire into natural phenomena such as virulence. To phrase it differently, although it has been widely recognized that the definition of virulence often depends on whether the scientist is a microbiologist, an epidemiologist, a parasitologist, a plant biologist, a zoologist, an immunologist, an evolutionary biologist, etc. (Alizon et al. 2009; Read 1994), it has largely gone unnoticed that this state of affair results mainly from different measuring techniques. This section provides a brief overview of how the concept of virulence is used in different scientific fields.

The way scientists talk about virulence is linked to the way they measure it, or assess it. Even when technical means of measuring were lacking, observations (e.g. symptoms, mortality) could allow classification of a disease as being virulent or not. As already mentioned, the most straightforward measure of the virulence of a disease is host's death. Lesions can also be used to determine the level of virulence (e.g. myxoma virus in rabbits; see chapter 4) but unless they can be ranked quantitatively, they provide only a rough estimate of the degree of virulence in a (viral or bacterial) strain (Stuart-Harris 1960, 12). Host's death, however, provides a reliable, if crude, method of measuring the virulence of a bacterial or viral strain.

As Thomas and Elkinton advanced, what matters in defining pathogenicity and virulence is that they should "yield explicit ways to measure them" (2004, 149). As an example of this, they remark that insect pathologists and vertebrate pathologists have long equated virulence with LD_{50} and LC_{50}. The former refers to the dose required to kill 50% of the insects that are being exposed to the pathogen. This is either done via injection of exposure to the pathogen during bioassays. The latter concerns the time (estimated) to kill 50% of the animals. When bioassays are done by exposing organisms to a pathogen, then the LD_{50} measure inevitable includes transmission (from one host to another), as Thomas and Elkinton pointed out (2004). This, however, conflicts with another prominent way to assess virulence developed by evolutionary ecologists, especially May and Anderson (chapter 4 and 6). According to them, there is a trade-off between the level of virulence and the transmission of the pathogen. Yet the coupling

between virulence and transmission makes little sense, Thomas and Elkinton argue, because transmission is an intrinsic aspect of the LD_{50} measurement technique. Plant pathologists, therefore, measure virulence not in terms of "damage" caused to a host (like zoologists and physicians do) but in terms of "transmissibility", i.e. the "capacity to infect" (Sacristan & Garcia-Arenal 1999, in Alizon et al. 2009, 249). Thomas and Elkinton noted that no matter how virulence is measured and defined it inevitably depends on the interaction between host, pathogen, and the environment (2004, 149). More importantly, a virulent disease does not always lead to the death of its host but to a recognizable set of symptoms and signs. How then can scientists measure virulence if the only available criterion was host's death or the time needed to achieve it? As Hull noted, very often scientists are silent as to how they operationalize their concepts – they just do it.

In order to ascertain the virulence of pathology a physician collects information, for instance by observing the symptoms of the patient. Medical doctors generally describe virulence, therefore, in terms of host's (i.e. patient) damage or "pathogenic effect" (Combes 2010), not in terms of the properties of the infecting agent, or in terms of host's death. In order to provide a more reliable measure that combine both the pathogen's biology and the host's immune response on the one hand, and that take into account the fact that most infections are not fatal on the other, microbiologists Casadeval and Pirofski have used the concept of "damage" as the "operational construct to define virulence and immunity" (2001, 341). For them, virulence relates to the relative capacity of a pathogen to induce damage and pathogenicity refers to whether the pathogen possesses this capacity, or not (1999).

Other scientists can also be interested in measuring virulence but no so much in the development of the disease in the host. Typically, evolutionary biologists and ecologist will equate virulence with the measure of pathogen's fitness. In turn, the measure of fitness can be the one of the host or the one of the pathogen but they are most likely to be concerned with pathogen's one but it needs not always be the case. For example, while botanists (Burdon 1987 in Read 1994, 73) emphasize pathogen's fitness (where virulence means the 'infective capacity' of a pathogen), zoologists generally define virulence in terms of the "reduction in host fitness caused by pathogens" (Frank 1993, in Read 1994). When virulence is measured as the effect on host's reproductive success (or

fitness) like in evolutionary biology there may not even be observable damage (or symptoms) on the host. This definition is thus distinct from the one used in medicine. Indeed, if one defines pathogenicity as the capacity of a pathogen to cause damage in a host, and virulence as the relative degree of this capacity then a pathogen can be highly pathogenic (interferes with the host reproductive success) but of low virulence (causes little damage). So pathogenicity and virulence "need not co-vary, although they often do" (Ulvestad 2007, 157).

It was long recognized that measuring virulence can be done at (at least) two levels: whole populations and individual level (Stuart-Harris 1960, 4). At the population level incidence and mortality from infectious diseases are often taken as indicators. Tables of mortality provide essential quantitative information about the virulence of a particular disease during an epizootic outbreak. These measures of the virulence of an epidemic must be weighed with a number of variables including age and previous exposure to the disease – which can lead to immunity and thus to the idea that the disease is less virulent. So when a disease changes in incidence it is problematic to assert whether this change results from a modification of the infectious agent or to a variation in the host (Stuart-Harris 1960, 4). The phenomenon of herd immunity – i.e. level of immunity obtained at the level of the whole after vaccinating parts of the population – adds to the complexity of measuring virulence at the population level. At the individual level (medicine) virulence is defined on the basis of signs and symptoms, speed of infection and progression of the disease.

To sum up, virulence and pathogenicity are neither entities nor material objects in the conventional sense of the word; their magnitude cannot be directly assessed before some standards of comparing and measuring are provided. There are material supports of virulence, also called "virulence factors", or even "virulence genes" and "pathogenicity islands" (Kaper 1999). These concepts derive from what I call the "molecular vision" of virulence (chapter 5). Notwithstanding the fact that material conditions realize virulence in the host so to speak, the nature of virulence is better expressed as a relative property, than as a "thing" or an "entity". Broadly speaking, therefore, the concept of virulence is often defined operationally as an indicator or an observable measure of disease severity. These measurements vary and include, for example, the assessment of host mortality,

reduction in host fitness, tissue damage, and so on. Thus, success in providing a standard terminology for these concepts is complicated due to the fact that virulence and pathogenicity are operationalized in different and sometimes, incompatible ways. Virulence remains an almost purely operational concept, but this does not mean that it is "intellectually empty". As can be expected, this chapter does not end with a "better" or more "unifying" definition of virulence; on the contrary, the claim in this chapter is that virulence is best understood as an elusive phenomenon whose meaning does not derive from a precise definition but rather through a series of concrete operationalizations. Operationalizing concepts is a crucial aspect of scientitif practice and maintaining a concept in a state of flux contributes to its operationalization in distinct epistemic contexts.

CONCLUDING REMARKS

According to philosophic orthodoxy science can only progress thanks to the "systematizing function" of abstract theoretical terms. The operational role played by the concept of virulence in the late nineteenth century (and throughout most of the twentieth century) suggests, however, that this entrenched position in the history and philosophy of science should be amended. A more nuanced combination of theoretical and operational terms is needed to account for the development of fields such as bacteriology but also microbiology and immunology. Indeed, one of the key findings here is that in the case of virulence what happened is the opposite of what Hull described for genetics: the concept of virulence did not become fully theoretical but it's being operational did not lead the concept of virulence to fade out of scientific research either. It is precisely this operational aspect that empowered it to be enacted as a research tool. Let us not be mistaken however: the concept of virulence *did* acquire some theoretical content, for instance when it became embedded within an epidemiological model as a mathematical variable (with the trade-off model, see chapter 4). And yet, it retained at the same time its operational character (i.e. virulence still had to be measured to be heuristically useful and meaningful). The concept of virulence did not decrease in importance but remains one of the most central concepts of today's health sciences, particularly in the field of infectious diseases, but also evolutionary ecology, molecular

pathology and so on. The puzzle, then, is how to explain the persistence through time of scientific concepts once believed to be inapt in contributing to the growth of knowledge.

In this chapter, I have argued that a straightforward consequence of applying operational analysis is that it explains why general, all-encompassing accounts of concepts are harder than ever to obtain (if possible at all). In the present case, a unified and general account of virulence (and other related concepts like "pathogenicity") as some are seeking, that is, a concept that would cover the meaning of these terms across disciplinary boundaries and over time, is highly improbable due to the fact that such concepts are operationalized differently within and across disciplines. This, however, is not problematic for operational analysis once it is acknowledged that "concepts in flux" (Elkana 1970) are also generative of scientific growth, whereas static definitions of scientific terms may be much less adequate to fit the different needs and goals of particular research programs. Moreover, although biologists worry that because virulence and pathogenicity are defined in different, non-overlapping ways – a situation, they think, can cause confusion (Thomas and Elkinton 2004, 146) – appealing to the measure of virulence on a case-by-case basis allows for disambiguation, while retaining the epistemic value of concepts "in tension" to use Falk's expression (2000).

To conclude, I would like to return briefly to Mendelsohn's comments mentioned in the opening of this chapter. There are two ways of interpreting his claim that virulence is an "operational concept" (2002). Firstly, if one understands Mendelsohn in the sense that the concept of virulence lacked a precise definition, then yes, it was an "intellectually empty" concept. It should be noted, however, that taken in this sense the concept of virulence is *still* as "empty" as in Pasteur's time, because it is vague, not well defined and that its significance is constantly negotiated and debated by microbiologists and evolutionary biologists, among others. If, however, one sees this concept "in action" so to speak, then this judgment is unwarranted. As I understand it Mendelsohn probably has the second option in mind: for him the concept of virulence does not derive its meaning from a set of clear-cut definitions but rather through a series of concrete operationalizations. This last point goes together with Canguilhem's remark that scientific practice is constantly re-shaping the concepts it uses in different contexts, and that such changes are then reflected in the scientific practice itself. Because of the

changing nature of scientific knowledge, however, one should not expect the meaning of scientific concepts to be transparent, well-defined and constant, contrary to what many philosophers have sought. Scientific objects, as Rheinberger has argued in his reply to David Bloor, function as such "by virtue of their opacity, their surplus, their material transcendence" (2005, 406). The operational aspect of the concept virulence indicated by Mendelsohn vindicates this point and opens up a space for the development of a history and philosophy of science that is more in tune with the intricate and dynamic relations between scientific practice and the formation of concepts.

CHAPTER 4: THEOBALD SMITH AND THE "LAW OF DECLINING VIRULENCE": SHIFTING PERSPECTIVES ON THE EVOLUTION OF DISEASE – 1880-1980

INTRODUCTION

Why do pathogens harm their host? Analogue in some ways to the broader, and somewhat older, question of "why do diseases exist?" this question is recurrent in evolutionary ecology.[86] Pathogens, to be sure, often bring about debilitating effects in hosts in ways that suggest a biological paradox. While exploiting their resources, pathogens frequently destroy their hosts, for instance during an infection. Although the annihilation of the host by the pathogen could be depicted as a crude example of "the survival of the fittest", situations where the host dies often amount to a "pyrrhic victory" for the pathogen (Lederberg 1988, 349), however, because colonies harboured by the host will die with it, a most intriguing phenomenon from an evolutionary standpoint.[87] Both species, indeed, share the same evolutionary fate as most pathogens need a *living* host to reproduce their kind. Living at its neighbour's expenses, a parasite is analogue to "a poor person who needs help to survive, but who nevertheless does not kill its chicken in order to have the eggs" (Van Beneden 1885, quoted in Alizon et al. 2009, 246). In killing the host (too fast) the pathogen runs the risk of jeopardizing its own transmission and reproduction, a situation some have regarded as a form of biological suicide (Grmek 1969). A dead host is thus, from a pathogen's point of view, something of an evolutionary dead end.

The destruction of the host by the pathogen during infection raises important questions for evolutionary biologists. In effect, why would natural selection favour high virulence if this inevitably results in both the host and the pathogen's deaths? How could the evolution of parasites even be conceivable should organisms die before passing down

[86] For recent discussions see Alizon et al. (2009); Kirchner and Roy (2002); Bull (1994).

[87] The terms parasite, pathogens, and infectious disease are frequently used interchangeably in ecology, population biology, and evolutionary theory to describe organisms living at the expense of others, often at the host's detriment.

their genetic, hereditary material to their offspring? Very much along these lines, infectious diseases – a form of predation often fatal to hosts – have become understood in the first half of the twentieth century as being temporary biological accidents, or transient pathological states, which will naturally decline given enough time.[88] *The Lives of a Cell* of British physician and science writer Lewis Thomas (1913-1993) reflected this conviction that "there is nothing to be gained, in an evolutionary sense, by the capacity to cause illness or death" (1974, 77). For Thomas, disease is a natural but contingent phenomenon, one that "usually results from inconclusive negotiations for symbiosis, an overstepping of the line by one side or the other, a biologic misrepresentation of borders" (1974, 76). In other words (infectious) diseases are either indicative of an imperfect or incomplete Darwinian adaptation between hosts and pathogens, or reflect the situation of a pathogen which has gone astray, venturing into a new ecological niche where it is only poorly adapted.[89] But in the natural world, Thomas continued, "pathogenicity is not the rule" (Thomas 1974, 76). Thomas' views on the nature of disease as evolutionarily contingent were once widespread among medical scientists.[90]

While host's death from communicable (or infectious) diseases frequently occurs worldwide, and particularly so in developing countries, scientists have long argued, however, that Nature is not always red in tooth and claw but also exhibits an opposite (evolutionary) tendency to Darwinian competition, one where hosts and pathogens naturally co-evolve towards mutual tolerance. Opposing Thomas Huxley's "gladiatorial" view of nature as wholly governed by the law of natural selection, anarchist Russian scientist Peter Kropotkin, for instance, argued at the turn of the twentieth century that "mutual aid" is a crucial "factor in evolution" (Borello 2004; Sapp 1994). Relying on Darwin's concept of an "entangled bank", those who emphasized cooperation over conflict and competition have tended to describe organisms' ecological interactions in terms of "uneasy equilibrium" or "unstable balance" (Burnet 1940, 13; Crist and Tauber

[88] For classic statements of a natural decline of infectious diseases see Cockburn (1963); Smith (1921).

[89] Following Smith, Hans Zinsser also urged that infectious diseases should be regarded as the "result of parasitism in which no such mutual adaptation has taken place" (1906, 8).

[90] For examples of the concept of infectious diseases as biological accidents, see Elek (1959, 313); Burnet (1946, 126).

1999; Park 2006). For, during the last century, most biologists considered that, all else being equal, pathogen's evolution towards harmlessness should be the expected outcome of long-term associations as it would benefit the host as well as the pathogen, thus ensuring the survival of both species (for references: Ewald 1994).

"Given enough time", microbiologist René Dubos said, "a pacific state of coexistence eventually becomes established between any host and any parasites" (1965, 190).[91] Similarly, for Frank Macfarlane Burnet (1889-1985), an Australian immunologist and Nobel Prize winner, "it is self-evident that if both host and parasite are to survive, a mild, rather long-lasting infection, which does no serious damage to the host and provides adequate opportunity for the parasite to be transferred to other hosts, is the most advantageous relationship for both" (Burnet 1953, 176). Hosts and parasites, in the long run, are expected to become adapted to each other so that only minimal harm is felt on both sides. Rephrasing an idea he borrowed from American bacteriologist Theobald Smith (1859-1934), the Dutch parasitologist N.H. Swellengrebel stated at about the same time that "the efficient parasite is a non-pathogenic organism", avoiding both "harm to its host as well as to itself" (Swellengrebel 1940, 466).

Nowadays dismissed as an example of "naïve adaptationism" (Sober and Wilson 1999, 43; Ewald 1994), this conventional wisdom was, however, widely accepted by some of those who pioneered the development of bacteriology, immunology, ecology, and the modern evolutionary synthesis in the twentieth century, up until the early 1980s, orchestrating an "ecological vision" of infectious diseases (Anderson 2004).[92] The conventional wisdom, moreover, "helped to spread the idea that virulence is subject to evolution" (Sigmund et al. 2002, 3), on the one hand, acting as an impetus to think about disease in broad ecological and evolutionary terms, on the other. Indeed, it provided an

[91] For Dubos "it is not very enlightening to say of a particular microorganism that it has a high or low virulence. A more meaningful statement is that a given pathogen is generally highly destructive in a given population when the pathogen and population come into contact, and *the severity of the infectious process tend to decrease* as contact between the two components of the system is continued over several generations (Dubos 1965, 165; emphasis added).

[92] The expression "conventional wisdom" was first used by epidemiologists May and Anderson (1983) to characterise the received, and rather unidirectional view of host and parasite co-evolution towards harmlessness.

explanation of one of the largest natural experiments in evolution: the decline of virulence in the myxoma virus among Australian rabbit populations during the 1950s and 1960s (Fenner and Fantini 1999). First extremely deadly, the virus evolved within a few years only towards intermediate levels of virulence: hypervirulent strains rapidly reproducing its kind killed the host too fast, whereas mild strains causing only minor, unsustainable infections failed to transmit to new hosts. Together, these ecological factors fostered the evolution of strains of intermediate virulence (Fenner 1983). Yet despite the broad acceptance of a natural decline in virulence over time and the evolution of harmless relationships between species, a comprehensive study of those who supported it is still lacking. Taking a somewhat different approach, the present chapter traces the history of the concept of virulence, as seen through the lens of this influential hypothesis, across disciplinary boundaries, linking biomedical concepts and practices throughout twentieth century's life sciences.

FROM THE CONVENTIONAL WISDOM TO THE TRADE-OFF MODEL

Although "intuition suggests that parasites should evolve to be benign whenever the host is needed for transmission" (Bull 1994, 1423), most biologists writing on the ecology of host and pathogen interactions nowadays advocate the mathematical model of the trade-off developed in the late 1970s (Alizon et al. 2009).[93] This more recent model is based on the idea that pathogens face several compromises (or trade-offs) between the mode of transmission and the degree of disease severity (i.e. virulence) they can inflict upon their hosts without compromising their own (evolutionarily) interests. These ecological constraints, on the one hand, interfere with the assumed tendency towards harmlessness, and the competition between different strains within a single host (i.e. multiple infections), between-host competition, and host's recovery rate, on the other, supply additional complexity for epidemiologists to consider when constructing ecological models of infections (Alizon and van Baalen 2008). Balancing the level of virulence

[93] The trade-off model was challenged some years ago, however, on the grounds that it was, on the one hand, too general to permit the development of realistic virulence management strategies (models should be "species-specific") and because it was too "simplistic", on the other (Ebert and Bull 2003). For a recent discussion of the model as formulated by May and Anderson, from a philosophical point of view, see Thompson (2011).

between host and pathogen the way the avirulence model suggests, thus, is not always feasible and is not regarded anymore as the expected, natural outcome of evolution by natural selection. Empirical and theoretical evidence suggests, on the contrary, that for a parasite to be successful evolutionarily, many paths or coevolutionary endpoints are possible (May and Anderson 1983). This more recent approach underpins the development of programmes on virulence management seeking to redirect pathogen's virulence by intervening, for instance, at the level of disease transmission (Dieckmann et al. 2002).

One of the main differences between the two models sketched above is that, on the one hand, there is no obligate evolution toward avirulence in the latter and that virulence is a trait that can either increase, decrease or become stabilized at intermediate levels as a result of the interactions between different factors and selective pressures. In sharp contrast with the most fundamental assumption of the conventional wisdom, on the other, the trade-off model claims that novel biological associations between distinct species will tend to be *less* virulent, *less* fit, and overall *less* infectious over time (Ebert and Herre 1996; Ewald 1994). The shift from one model of disease evolution to another raises important historical and epistemological questions: When, and in which context, was the avirulence model initially advanced? What are the factors that fostered the development of a new, mathematically-oriented model during the late 1970s? Following the rise of this new model of disease evolution, can we identify significant changes in the concept of infectious disease itself? Is a new understanding of the concept of virulence emerging altogether? I return to the question of the transition between the two models in the conclusion and I suggest that despite the fact that biologists consistently oppose them, one can still detect significant conceptual continuities between these models. What the change from the avirulence hypothesis to the trade-off model firmly established, however, is that the former is only a special case of the latter and not a general model of disease evolution, as many have assumed in the past century.

Beginning with a short description of the avirulence model, I will then contextualize the debate on the nature of virulence by relating this concept to some key issues in the life sciences and public health during the late nineteenth century such as the cause(s) of epidemic disease, the evolution of germs and the concept of disease specificity, as they

began to be addressed in the light of evolutionary theory. Replacing Smith's contributions within bacteriology, and particularly his study of cattle fever, within the broader context of public health medicine, and evolutionary thinking I will trace the history of the avirulence hypothesis from the work of Smith up to its widespread acceptance in the mid-twentieth century, and until its downfall in the 1980s. Exploring this theoretical rearrangement in virulence studies not only illuminates an important episode in the history of disease transmission that remains largely uncharted in recent scholarly anthologies (e.g. Gaudillère and Löwy 2001), but also sheds light on the intermingled relationship between evolutionary biology, ecology, and medical bacteriology in the past century, while providing at the same time a much needed initial appraisal of Theobald Smith, a forgotten figure in contemporary U.S. medical history. Building on the work of historian of science J. Andrew Mendelsohn (2002) this article also supports the view that the category of "virulence" in biomedicine occupied a central (but neglected) place in the establishment of a number of disciplines in the life sciences during the past century.

A LASTING MODEL OF HOST-PATHOGEN (CO)EVOLUTION

During his Presidential Address to the Western Society of Naturalists at Stanford University on "Parasitism and Evolution" the American zoologist Gordon H. Ball summarized the then-prevalent ecological model of host and pathogen interactions with remarkable clarity, and stressed its evolutionary dimension: "I am referring to the view that pathogenicity to the host is really a disadvantage to the parasite and that consequently, long-standing parasites, by the *process of evolution*, have much less of a harmful effect on the host then have recently acquired ones" (1941, 345; emphasis added). Where this view comes from, Ball confessed, was difficult to determine precisely, but he suggested that "perhaps van Beneden (1809-1894) in his *Animal Parasites and Messmates* of nearly 70 years ago was one of the first to set forth the view [of the avirulence model] fairly definitively" [...] (1941, 346-7). In the last quarter on the nineteenth century, amidst the rise of several social associations in Britain and France, such as trade unions and mutual aid associations (*mutuelles*), Van Beneden coined the biological concept of "mutualism". Unlike his son Edouard who was openly Darwinian, Pierre-Joseph van Beneden believed in the theory of special creations (Hamoir 1999). He

remained, indeed, a "lifelong opponent of the view that evolution resulted from a 'struggle for life' and natural selection" (Sapp 1994, 20). For him, mutualisms such as plovers eating leaches from crocodiles' teeth or lichens (composed of a fungi and an algae), are the result of God's benevolent intent: "All these mutual adaptations are pre-arranged" van Beneden said, "and as far as we are concerned, we cannot divest ourselves of the idea that the earth has been prepared successively for plants, animals, and man" (1875, xxvii, quoted in Sapp 1994, 18). As was already mentioned, however, the avirulence hypothesis is an *evolutionary* model of disease, and thus van Beneden cannot strictly speaking be pictured as its precursor, despite Ball's suggestion.

In contrast, and notwithstanding the importance of Van Beneden's concept of mutualism, the work of American bacteriologist Theobald Smith stands as a much more likely candidate for the origin of the avirulence model. In effect, not only have several biologists pointed out that "the evolution of a disease tends toward development of a symbiotic relationship" (Bang 1959, 352) was an idea initially proposed by Theobald Smith, but Smith himself formulated an evolutionary hypothesis he came to call "the law of declining virulence and advancing parasitism" (Smith 1904). The novelty of this perspective on disease evolution was immediately recognized by medical doctors, although some identified predecessors. Ball himself believed that "Theobald Smith did much to popularize it (1921) and to apply it to modern concepts of epidemiology" (1941, 347). Smith's views remained largely unchallenged for about eighty years and they profoundly contributed to the development of other fields outside medical pathology and parasitology. In addition to his views about a natural decline in infections over time, his concept of "evolving parasitism" and his "law of declining virulence" were influential in immunology, bacteriology, virology, epidemiology, and public health medicine.[94]

In the past century, scientists frequently turned to Smith as a point of departure for discussing host and pathogen interactions and coevolution.[95] For example, the

[94] In addition to renowned virologists like Burnet and Fenner, prominent epidemiologists like Major Greenwood, in England, and Simon Flexner, in the U.S., endeavoured to study epidemics along the evolutionary lines as promoted by Smith (Anderson 2004; Mendelsohn 1998).

[95] See Musgrave (1908); Zinsser (1914); Swellengrebel (1940); Ball (1941); Dubos (1959); Bang (1959); Andrewes (1960); Lederberg (1993); Ewald (1994); Alizon et al. (2009).

"philosophical statement" of disease evolution attributed to Smith is "to a large extent true", epidemiologist and virologist Frederik Bang concedes – and it applies paradigmatically to the case of myxomatosis –, even if it admits a number of exceptions, however (Bang 1959, 352). A few years before, during a Ciba symposium on Virus, Virulence and Pathogenicity, the British virologist Christopher H. Andrewes, co-discovered of the viral nature of influenza (Smith, Andrewes, Laidlaw 1933), had remarked that "nowadays we all accept Theobald Smith's dictum that the natural tendency of a host-parasite relationship is towards a mutual tolerance which will permit a survival of both partners" (1960, 34). Andrewes's comment did not elicit any questions or critical remarks during the discussion that followed, quite to the contrary (see pp.39-42).[96]

This should not be surprising since Macfarlane Burnet (who chaired the meeting) provided influential support to this view from the mid-1930s onward, emphasizing the role of the environment as a powerful determinant of health and disease. Working on psittacosis, a disease affecting mostly parrots held in captivity, Burnet was struck by the fact that when living in the wild, the animals were sometimes seriously infected with psittacosis viruses without, however, displaying any disease symptoms (Park 2006, 511). The healthy carriers (parrots) and the virus had learned to cohabit, developing a state of "stabilized equilibrium" or "mutual tolerance" over the course of many generations (Ibid.) In *Virus as Organism* Burnet wrote (still without referring to Smith) that "the normal end result of long-period interaction under approximately constant conditions between host and parasite is a state in which the host suffers no significant disability and the parasite persists long enough to ensure transfer by one or other method to a new susceptible host" (1946, 26).[97] Once formed, however, this fragile, inter-species ecological equilibrium could easily be disturbed should the environmental conditions come to change too radically, upsetting the delicate balance slowly brought about by evolution.

[96] In his address Andrewes took some careful distance with Smith's (and Burnet's) model, however, remarking that natural selection does not necessarily favour the least possible virulent virus, but rather an "intermediate, optimal virulence" (1960, 36).

[97] Many who shared Theobald Smith's idea on declining virulence, including Burnet, Dubos, Fenner, and Lederberg, knew each other personally but often failed to quote each other's work (Anderson 2004). In his autobiography Burnet confessed having read Smith's *Parasitism and Disease* only *after* he published his own book on infectious disease (1968, 23).

More recently, in the opening chapter of *Emerging Viruses*, the Australian microbial geneticist Josh Lederberg (1925-2008), also Nobel Prize winner, remarked that "since Frank MacFarlane Burnet, Theobald Smith, and others [...] we have understood that evolutionary equilibrium favours mutualistic rather than parasitic or unilaterally destructive interactions. Natural selection, in the long run, favours host resistance, on the one hand, and temperate virulence and immunogenic masking on the parasite's part, on the other" (1993, 3).

An important insight deriving from this model is that the observable level of virulence is linked to the length of the biological association between two species: virulent associations are phylogenetically recent, whilst benign ones are much older. As Ball (1943) suggested, the level virulence came to be seen as a reliable temporal marker of the length of biological associations. For example, according to Asa C. Chandler – author of an *Introduction to Human Parasitology* (1936) – "a high degree of pathogenicity may be considered *prima facie* evidence of a recent and still imperfect development of the host-parasite relation" (quoted in Ball 1943, 346). The same year, H.B. Fantham asserted boldly that "a parasite pathogenic to its host is considered to be relatively new to it", concluding that "in parasites long resident in their hosts, a *mutual state* of *harmony* or tolerance is set up to a greater or less degree", and that "the newer parasite is to its host, the less is the *harmony* that exists between them" (Fantham 1936, 324 in Ball 1943, 348; emphasis added). This model eventually boils down to the idea that infectious diseases result from an incomplete Darwinian adaptation between two organisms which, on an evolutionary timescale, have only recently been brought together.

It is only by the end of the nineenth century and the birth of bacteriology that the concept of virulence moved to central stage, contributing to the development of several fields of research in the first half of the twentieth century. On the one hand, experimental changes in virulence in microorganisms and host's resistance provided an explanation for the severity of the disease during epidemics; on the other, such modifications could also account for the creation of novel diseases (i.e. originating de novo). In addition, the old medical concept of disease specificity was re-defined through an evolutionary lens, fostering at the same time a new understanding of infectious diseases as historical (i.e. evolved) entities. Examining these entangled issues will provide both a scientific and

philosophic background for an in-depth discussion of the work of Theobald Smith, and in particular his concept of an "evolving parasistims" and his law of "declining virulence", which can be seen, in part, as a response to these problems.

THE CONCEPT OF VIRULENCE IN THE LATE NINETEENTH CENTURY: EPIDEMICS, GERMS, AND SPECIFICITY

EXPLAINING EPIDEMICS: THE SEED AND THE SOIL PERSPECTIVES

Between 1880 and 1920, bacteriologists and epidemiologists emphasized different causes as being responsible for the waxing and waning of epidemics: while bacteriologists's explanations postulated changes in the germ's virulence, epidemiologists focused on changes in the environment instead (Amsterdamska 2004). This epistemological quarrel notwithstanding, causes of epidemics began to be more precisely circumscribed with the recognition that germs are causal agents of disease, although epidemiologists continued to insist that "laboratory bacteriology is not the conclusion of the whole matter" (Crookshank 1920, 183). The work of Robert Koch and Louis Pasteur, primarily structured by the *concept* of virulence, and not by a general *theory* of infectious diseases, provided such links between disease processes and microorganisms (Mendelsohn 2002). Disease-causing power in microorganisms, however, varied widely, and Pasteur and his colleagues knew that the virulence of a microorganism could be experimentally enhanced or decreased, through serial passages in a host. Since these induced modifications could be passed on to the next generation changes in virulence became associated to the issue of the inheritance of acquired characteristics and the possibility of pleomorphism (i.e. the thesis that there are no bacterial species).

Although changes in virulence had sometimes an unmistakable Lamarckian gloss, especially in laboratory contexts, [98] they were, however, also frequently interpreted from a Darwinian point of view. In Britain, for instance, the concept of evolution by natural selection fostered new, genuine explanations of virulence during epidemic outbreaks. In an insightful paper on "infection considered from a Darwinian point of view" (1878),

[98] On the history of this question in France see Gayon (1995).

London Medical Inspector Hubert Airy (1838-1903) suggested that the germ theory of disease recently developed by Pasteur and Koch addresses a "complex problem of natural selection" (1878, 253) involving two "interdependent" variables: "man and microzyme". Foreshadowing the avirulence model, Airy argued that through the course of generations there is a general tendency toward "asusceptibility" to particular diseases provided that the least susceptible individuals are more likely to survive and to reproduce successfully, passing on the resistance capability to their offspring. While human populations is likely to evolve toward greater "asusceptibility" the parasite will, however, "step by step attain new virulence" (1878, 254). According to Airy the "fatality and virulence" of "nearly all the outbreaks of pestilence" such as this one are due to the fact that the "constitution of the race has not had time or opportunity to adapt itself" (1882, 255). This ongoing process of "parasitic adaptation", Airy argued, is liable to an eventual "compromise" by means of natural selection which will maintain both the host and the pathogen alive and with sufficient variation of each side. Fiji Islanders, for instance, when were first exposed to measles, became severely diseased as they lacked appropriate level of immune protection European communities had developed following a prolonged contact with the malady. Assuming that hosts and pathogens populations co-evolve toward equilibrium allowed Airy to explain why Fiji Islanders were more susceptible than other populations to particular pathogens: natural selection did not have enough time to fit "man and microzyme" together, but might eventually do so.

BIOLOGICAL VARIATION IN DISEASE AND RETURN TO TYPE

The role of germ's virulence in causing epidemics relates to another one frequently framed in terms of whether diseases can change or return to their "original type", for instance following environmental changes. The work of Williams Roberts (1830-1899), who was M.D., Fellow of the Royal College of Physician and Fellow of the Royal Society, provides an interesting case of such approach to virulence. Before delivering an address at the British Medical Association meeting in 1877 in which he ventured an explanation of why two bacteria apparently alike in both their morphological and physiological aspects can cause different diseases, Roberts wrote to Charles Darwin, with whom he used to

correspond regularly, to inquire about the possibility for a harmless bacteria to produce (or "sport") a pathogenic form (quoted in Bynum 2002, 61).

According to Roberts, Darwin's "laws of variation seem to apply in a curiously exact manner to many of the phenomena of contagious diseases". One of these laws, he continued, is the vertical transmission of a variation from parents to offspring; another "law", however, is the tendency for a given variation "to revert once more [...] to the original type" (quoted in Nash 1915, 81). [99] By means of the concept of "reversion to original type" Roberts (1877) wanted to explain outbreaks of disease like cholera. If germs are living organisms, he reasoned, then a highly virulent bacterium could under specific environmental circumstances revert to the original "non-parasitic" (saprophyte) type of its species (explaining the decrease in virulence) and similarly, an avirulent bacterium could sport a virulent and pathogenic form (explaining the outbreak of an epidemics). Roberts argued that if "contagia were organisms" then they must exhibit variation, including in their potential to cause disease. His key example was *Bacillus subtilis* (used by Pasteur in his experiment on spontaneous generation) and *B. anthracis* (the bacillus causing anthrax), two species of bacteria which, according to the microbiologist Ferdinand Cohn were identical "in form and development" despite producing different pathogenic effects (Bynum 2002).

Using an analogy with plants to explain this transformation Roberts saw "no more difficulty in believing that the *B. anthracis* is a sport from the *B. subtilis* than in believing, as botanists tell us, that the bitter almond is a sport from the sweet almond – the one a bland innocuous fruit, and the other containing the element of a deadly poison" (Robert 1877 in Bynum 2002, 61). He thus believed that bacterial species could evolve into new diseases, for instance as a function of the type of environment (or "soil") in which the germ is planted. Hereditary changes in bacterial types, however, were seen as going against the older idea that diseases have specific causes, an idea which underwent significant challenges from an evolutionary standpoint in the last two decades of the nineteenth century.

[99] On the concept of reversion to type in evolutionary biology see Gayon (forthcoming).

Despite the possibility for germs to undergo significant transformations of evolutionary nature it was also clear that diseases (and so, germs) did maintain some of their key characteristics over time. For Armand Trousseau (1801-1867), an influential French physician who placed the concept of specificity at the core of medical practice, diseases have "specific characters, absolute and invariable, distinguishing them from one another, irrespective of the gravity of the illness" (1873, 500). This absolute specificity, in turn, is aetiologically determined by its *morbific cause* (Ibid). The formulation of Robert Koch's postulates provided new support for the doctrine of disease specificity, i.e., the idea that each disease has a particular causative agent.[100] After Darwin, however, the question of biological variation launched several discussions and inquiries concerning the "evidence of *variability*" and the "*persistency* of type", not only in biology but also in public health, epidemiology, bacteriology, and medicine. For example, in Stevenson and Murray's treatise on *Hygiene* (1893) T.W. Thompson suggested that "the older notion of the absolute immutability of species being now indefensible, we cannot fail to be impressed by the variations from time to time exhibited by epidemics"; but on the other he urged that if "it is necessary to abandon the absolute immutability of diseases, it is of the utmost importance to avoid falling into the opposite error of underestimating the relative fixity of type which some of them have evidently acquired" (Thompson quoted in Hamer 1906, 32).

A decade later the epidemiologist William Hamer (1862-1936), a well-known critic of bacteriology, concluded his *Milroy lectures* with a plea for reconciliation in the explanation of epidemics between "the extraordinary persistency of disease types with the no less remarkable variability of the organisms to which the bacteriologist attaches importance as cause of disease" (1906, 72). This tension between persistence and variation also reflected political, even epistemological quarrels between bacteriologists and epidemiologists each of whom drew on distinct medical traditions and methods in order to explain epidemics (Mendelsohn 1998), emphasizing, on the one side, the

[100] Koch stated that "each disease is caused by one particular microbe – and by only one. Only an anthrax microbe can cause anthrax; only a typhoid microbe can cause typhoid" (Koch 1876, quoted in Evans 1993, 20).

constancy of the germ and the changing environmental conditions, on the other. At about the same time, however, the internal coherence of the concept of specificity began to be challenged on the basis of evolutionary theory.

RE-FRAMING THE CONCEPT OF DISEASE SPECIFICITY IN THE LIGHT OF EVOLUTION

William Collins, a London physician, was one of the first to openly question the concept of specificity from an evolutionary point of view asking, in *The Lancet,* whether "the theory of specificity" is not "swallowed up in the larger theory of evolution" (1881). After the publication of this short piece Collins wrote a longer essay on *Specificity and Evolution in Disease* (1884), dedicated to philosopher Herbert Spencer, [101] where he argued that the concept of specific diseases is

> But a reiteration in the language of Genesis that in the beginning were created the germs of specific diseases "each after his kind," that each has propagated itself in strict genealogy from that time to this; and if we are to follow Dr. W.B. Carpenter we must also believe that there were at the same time created specific susceptibilities to each and every one of these said diseases in our earliest progenitors, and ample provision made for the perennial perpetuation of the same (1884, 7).

Collins' argument was that once we accept the doctrine of disease specificity we have to believe that germs and predisposition to disease were created at the same time, a view he rejected as untenable. The core of the problem, however, and if we follow Collins, is that the theory of specificity "can never explain the *development* of specific diseases" (1884, 7; emphasis added), that is, their coming into being, or their emergence in individuals. Emphasizing the importance of the "soil" over the "seed", Collins called upon the theory of evolution to explain both the origin and the development of disease agents into recognizable, specific forms.

Collins' ideas about evolutionary pathology were not immediately accepted by medical doctors (see Collins 1920), but especially by bacteriologists. For instance, W.W.C.

[101] Spencer thanked Collins for the dedication of his essay, and regarded his conception as "thoroughly philosophical" in that it "promises to open the way to a considerable reform in pathology" (letter of Spencer to Collins, reprinted in Collins 1884).

Topley, then working at the Chairing Cross Hospital in London, argued that the spread of bacterial infection is better explained by postulating an increase of virulence by natural selection (1919), whereby a coevolutionary process hosts acquire progressive immunity and pathogens gain in virulence power. In his response to Collins, and trying to reconcile the notion of specificity with evolutionary thinking, Topley suggested that "an evolutionary hypothesis, in which especial emphasis is laid on changes in environment, does not exclude a belief in specificity, provided that this doctrine is not applied with an unintelligent rigidity" (1920, 1136). Yet even Collins, although he rejected the idea of an "absolute specificity", was open to the idea of a "relative specificity" which was, "as true as ever", once "rightly understood and studied in the light of evolution" (Collins 1884, 28). The evolutionary view advocated by Collins and others opened the door to the possibility that disease specificity can have a history of its own. In summary, the concept of virulence was, on the one hand, particularly useful in constructing explanations of a number of biological phenomena in the late nineenth and early twentieth century, including the nature of hereditary processes, bacterial variation and disease causation, especially during epidemic outbreaks. On the other, however, the concept of virulence had an even deeper impact as it troubled existing models of disease specificity, and provided alternative explanations based on individual constitutions, predispositions and evolution. In the next section I will examine how the work of Theobald Smith provided a way out to reconcile the concept of specificity with Darwinian evolution while at the same time proposing one of most important operational approaches of host-parasite interactions and infectious diseases.

THEOBALD SMITH: LIFE AND WORK

Theobald Smith was not awarded a Nobel Prize for having identified for the first time in medical history an arthropod-borne disease, but he was once regarded as one of "America's foremost bacteriologist" (Bulloch 1979, 398). Born in Albany from German immigrant parents, he did brilliant studies and obtained a scholarship to enter Cornell University in 1877. Trained as a pathologist "in the biology of the Darwin-Huxley tradition" (Zinsser 1936, 264) Smith was a scholar in natural history and medicine but was relatively ignorant of the new science of bacteriology (Clark 1961, 120), a field in which he

eventually made great scientific contributions. After graduating from the medical school, and supported by his mentor from Cornell, microscopist Simon Henry Gage (1851-1944), Smith obtained a position in Washington in 1884 at the Bureau of Animal Industry (B.A.I.) where he stayed until 1895, working under Daniel E. Salmon. Thanks partly to his knowledge of French and German that allowed him to read the original articles he quickly became acquainted with the methods of bacteriology developed by Pasteur and Koch which he introduced into the U.S. in the early days of bacteriology. From 1885 to 1915 he worked at the Harvard Medical School in Boston where he experimentally challenged the "absolute identity" of the tubercle bacilli affecting mammals and demonstrated that, contrary to Koch's claim, tuberculosis comes in both a human and a bovine type (Smith 1898). Finally, Smith assumed the directorship of the Rockefeller Institute of Medical Research in Princeton until the end of his life. Smith's work was respected by epidemiologists and bacteriologists and in 1933 he received the Copley Medal from the Royal Society of London for his "original research and observation on animals and man".

SOLVING THE TEXAS FEVER PROBLEM

Theobald Smith became especially renowned for his detective work on Texas fever carried on from 1886 to 1893 and published as *Investigation into the Nature, Causation and Prevention of Texas or Southern Cattle Fever* (Smith and Kilborne 1893). [102] Originating from Spain, West Indies and Mexico, the disease was possibly introduced by cattle brought to America during the seventeenth century (Doleman and Wolfe 203, 99). In South Illinois, in the summer of 1868, a particularly violent epizootic episode of cattle fever broke out causing the death of at least 15, 000 animals, in addition to substantial economical loss. An early report by the New York State Commissioner Dr. Cresson Stiles published the following year indicates that the kidneys of the sick animals "were deeply congested"; the urine was "of glutinous character"; and no red blood discs could be observed in the blood of the animals (in Dolman and Wolfe 2003, 103). Stiles died from a mental disorder in 1870 and his analyses were left incomplete, however. During the ten

[102] The controversy regarding the precise role of Kilborne in this episode or the decision of Salmon to include his own name on the report cannot be examined here (see Dolman and Wolfe 2003, chapter 6).

years following the outbreak of cattle fever, reports on the nature and the causes of the disease were regularly issued. Although the observations and conclusions differed to some extent, most of them dismissed the "tick theory" as a ludicrous, implausible explanation of the mode of transmission of the disease (Dolman and Wolfe 2003, 101; Haygood 1986, 555).

Smith turned his attention to the aetiology of cattle fever in September 1886, when the spleen of two animals who died of the disease was delivered at the B.A.I. The autopsy performed on the enlarged organs revealed that one of them showed "in or on many red corpuscles small round bodies, perhaps 1 μ in diameter [...] which stain poorly in an aqueous solution of methyl-violet, very well in aniline-water methyl-violet". These bodies "resemble micrococci in size and form". When "unstained they can be seen as mere transparent spaces in the corpuscles" (Smith and Kilborne 1937, 345). Upon embarking on his research into the cause of Texas fever, after reviewing the available evidence, Smith considered three plausible hypotheses (Ibid. 430). According to him, the disease could

1- Have a bacterial origin, with bacteria producing toxins acting directly on the blood corpuscles of the animals.

2- Result from the production of a toxic substance by bacteria multiplying in the intestinal tract of the host and dissolving the red blood cells.

3- Be the result of a microparasite invading the red blood cells, destroying the corpuscles.

With great precaution, Smith concluded after a large number of precise histological microscopic observations that Texas fever was not caused by a bacterium but by a microscopic protozoan (*Pyrosoma bigeminum*) which grows inside red blood cells and ultimately destroys them.[103] He warned that diagnostic of cattle fever should go beyond the signs and symptoms and be made by the counting of the red corpuscles, the physiological changes these typically undergo during infection, and the presence of the parasite, established through microscopic examinations. Figure 1 represents the different

[103] Nowadays biologists have reclassified this organism as two distinct species belonging to the genus of *Babesia*: *Babesia bovis* and *Babesia bigemina* (Haygood 1986, 556).

forms Texas-fever parasite can take when stained with methylene blue, and figure 2 shows the technique to obtain blood sample on cover glasses.

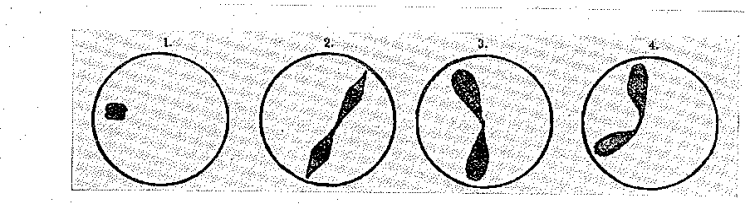

Fig. 1 Intraglobular forms of the Texas-fever parasite (Smith and Kilborne 1937, 449).

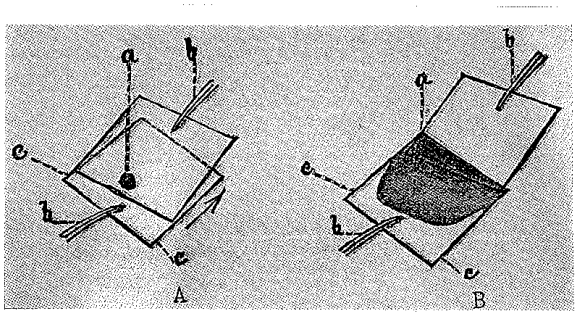

Fig. 2 Methods of preparing blood on cover glasses (Smith and Kilborne 1937, 415).

Smith announced his preliminary findings regarding the causative agent of Texas fever at the Annual Meeting of the American Public Health Association of the Brooklyn Institute in 1889 as follows:

> There is a continuous or paroxysmal destruction of red-blood corpuscles due to an intraglobular parasite, and the disease results mainly from the incapacity of the internal organs, primarily the liver, secondarily the spleen and kidneys, to transform and remove the waste products resulting from such destruction. In milder cases the protracted anaemia, which results from the loss of corpuscles, may become the chief cause of exhaustion and death (Smith, quoted in Dolman and Wolfe 2003, 105).

The causal explanation of the cattle fever still required the discovery of the mechanism of transmission of the disease, however. This ecological aspect of the problem Smith, Kilborne, and Salmon tackled was the following: when cattle from southern States – including South Carolina, Georgia, Florida, Alabama, Mississippi, Arkansas, Indiana, and Louisiana – which were apparently healthy, were taken to the northern States (Virginia, North Carolina, Tennessee), the northern cattle started to be decimated. Similarly, when northern cattle were moved to southern States, they soon started to become infected and died of fever and anaemia, despite the fact that southern cattle with which they interacted did not display any visible sign of disease. In contrast with the opinions voiced in the various reports on the cause of Texas fever, popular knowledge at the time was that this phenomenon was linked to the ticks with which the southern cattle were covered. In a manner similar to Edward Jenner (1749-1823) who learned from countrymen that cowpox could provide immunity to smallpox, Smith considered the tick hypothesis seriously.

THE TICK HYPOTHESIS

Designing disease transmission experiments at the B.A.I. Smith constructed enclosed fields to test the tick hypothesis as a possible vector of the disease. His experiments, beginning in summer 1889, aimed at answering three distinct but related questions: can Southern cattle transmit the disease to Northern cattle without the intervention of ticks? Can the disease transmit to Northern cattle in the absence of the Southern cattle? Can Northern cattle acquire the disease by having ticks artificially placed on them? (Smith 1937, 480) All possible combinations were carefully tested and explored thanks to the experimental fields Smith and his colleagues designed at the Bureau of Animal Investigation. Summarizing the results of the several experiments conducted in 1889, Smith concluded that a field must be infected with ticks for Texas fever to appear in the first place and also that this was sufficient to cause disease in Northern cattle in the absence of Southern animals. When Southern cattle from which ticks had been mechanically removed and tick-free Northern cattle were together placed in the same field, none of them developed (nor transmitted) the disease. The 1889 experiments established that Texas fever comes from the permanently infected territories (i.e.

southern States) and is transmitted by the animals up north through the ticks, maturing in the bovine and acting as a vector (fig. 3). “It took four years of slavery at the microscope, at autopsy, at watching ticks hatch from the egg” (Smith 1937, 346), but he finally established the complete life cycle of the parasite and identified the ticks as the vehicle of the disease transmission. Knowing that a vaccine against Cattle fever was unlikely to be developed because the microparasite “cannot be cultivated” (Smith 1937, 537), the discovery of the disease vector withheld significant public health consequences, for it meant that to eliminate or for cattle to avoid contact with the ticks could help preventing the parasite causing Texas fever to spread.

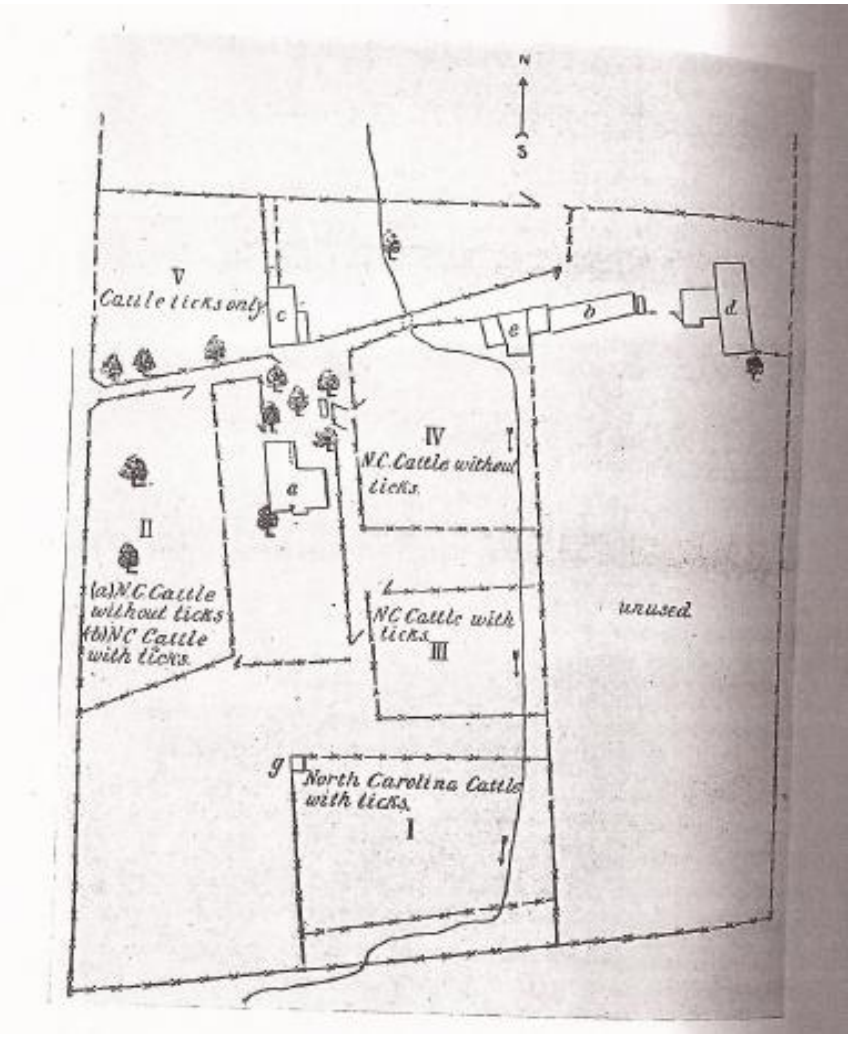

Fig. 3. Enclosed fields at the B.A.I for the 1889 experiments with Northern cattle covered with ticks (or not) to study the role of infested fields and Southern cattle in the transmission of the disease (Smith and Kilbourne 1937, 484).

The most fascinating epistemological point of the cattle fever episode, though, was perhaps not so much the discovery of how the disease was caused but rather "how apparently healthy animals could transmit a fatal disease to others?" (Haygood 1986, 558) The puzzle was about acquired immunity, a topic Smith was acquainted with from his previous work with Salmon (Salmon and Smith 1886). It was found that the protozoan present in the blood of northern cattle that causes disease is also present in the southern ones, with however no apparent pathological consequence on the animals. The Southern animals are immune to the disease, and this immunity last well beyond a few years (Smith 1937, 533). In contrast with northern cattle those animals living South are continually exposed to ticks bites, starting very early in life. Being repeatedly infected throughout their existence by several insects' bites southern cattle progressively developed a transitory form of acquired immunity that requires continuous attacks on the part of the ticks. "Eventually" as Haygood notes "a tenuous balance is reached" between the pathogen population thriving in the bloodstream and the immune system of the hosts (1986, 559). In Smith's words, "the repeated mild attacks to which they [young calves] are subjected finally makes the system indifferent to the virus" (1937, 555).

The cattle fever episode played a crucial role in shaping Smith's ideas about parasitism, evolution and disease, providing him with a concrete biological example of the harmlessness of a long-term association between an organism and its parasite. As microbiologist and biographer of Theobald Smith, Claude Dolman noted, Smith's contention that "the symptomatology of an invasive disease reflected the degree of disequilibrium in a host-parasite relationship" derives from his work in Washington where "mild cases and the carrier state proved to be missing links in the riddle of Texas fever" (1984, 578). Moreover, this experiment allowed Smith to generalize his views on disease and evolution understood in terms of both ecological and physiological "equilibrium". In a paper read before the first meeting of the Society of American Bacteriologist a few years later, Smith suggested that

> The mutual dependence of host and parasite upon one another as to the weapons which each will use to restrict the inroads of the other leads us to assume that the final result of continued association of a certain parasite with a certain host will be a delicate equilibrium which is

> dependent on the special nature of the bacterium, as well as upon the host, and is likely to continue unchanged as long as these two agents remain the same. The final definitive relationship furnishes us with the various types of disease which remain fairly constant from year to year, from generation to generation (1900, 106).

As this quote illustrates, Smith explained the constancy of disease patterns on the basis of the "continued association" between host and pathogens – just like in the case of the Texas fever. In turn, this results in the various "types of disease", each having its own specific and individual characteristics. Disease specificity, as defined above, started to be conceptualized not as something forever "given" but rather as the end product of a long evolutionary process. Solving the puzzle of cattle fever thus enabled Smith to put together an original *evolutionary* view of parasitism which was soon followed. [104] He explained changes in virulence not by providing a more fine-grained definition of the concept but by infusing evolutionary dynamic into it, and this evolutionary dimension provided the basis a "generalized parasitic theory of disease", to use John Farley's expression (1989). For Smith wanted to bring together "all alien invaders and parasites of the animal body and deal with them and the disturbances they produce under some unifying principle" (Smith 1963, vii).

THE LAW OF DECLINING VIRULENCE AND THE CONCEPT OF EVOLVING PARASITISM

Advocating the importance of looking at diseases from a biological standpoint, Smith warned that parasitism should not be regarded "as a pathological manifestation" per se but rather as "a normal condition, having its roots in the interdependence of all living organisms", and when some forms of parasitism bring about pathological effects those are only "incident in a developing parasitism" (1934, 2-4). Discussing the differences and the connections between various forms of parasitism and saprophytes (i.e. organisms feeding on decaying matter) Smith argued that the former evolved from the latter. According to Smith there is a spectrum onto which we can map the level of adaptation a parasitic species has reached, by looking at the extent to which such species can survive

[104] Musgrave (1909); Fantham (1936); Chandler (1940); Burnet (1946).

without the presence of a host ranging from the "strictly parasitic" forms of parasitism that cause "diseases which are very slow in their progress, often lasting for years and frequently checked and cure" such as tuberculosis, syphilis and leprosy (1887, 7), to the bacterial species that can survive without a host but which can cause great harm if they found themselves in the wrong environment. The mechanism by which parasitism evolves is "the universal struggle of living things" (1934, 19).

Smith suggested that the capacity for "living and multiplying upon dead matter" was an ancient adaptation and "that all pathogenic bacteria were derived by a *process of natural selection* from the innumerable harmless species everywhere peopling the air, the soil, and the water" (1887, 4; emphasis added). In other words, there is a natural, steady progression in the making of a parasitic and commensal way of life. Earlier in his career Smith also observed that "the better adapted the parasite becomes, the more compatible will it be with the host and the less capable of carrying on an independent existence" (1887, 7). Highly pathogenic bacteria, thus, are either "incomplete adapted parasites" or some kind of parasites which have "escaped from their customary environment" and are trying to adapt themselves to a new milieu, and "to establish some equilibrium between themselves and their host" (1904, 828). "The less complete the adaptation", he concluded "the more virulent the disease produced" (Smith 1904, 828). In the case of Texas fever the adaption between the ticks and the Southern cattle was optimally adjusted, generating no pathological effects whatsoever. To explain this progressive adaptation between host and parasite Smith relied on the concept of "balance" understood as an adaptive state established by the process of evolution by natural selection. For example, "the highly adapted microorganism which depends upon one host for its existence – as, for example, the still unknown smallpox organism – has through *natural selection* established between itself and its host a certain balance or equilibrium" (Smith 1921, 7; emphasis added).

Smith expressed his own views about the "law of a declining virulence" most clearly in a paper on the "Problems in the life history of pathogenic microorganisms" (1904, 832). Discussing the relations between different mechanisms for pathogens to invade, reproduce and escape the host, he reasoned as follow with respect to the idea that a pathogen would be disadvantaged (on evolutionary grounds) if it remains too virulent:

> In fact the more virulent the microbe, the more rapid the death as a result of invasion, the less the opportunity for escape. Hence there will be a *selection* in favour of those varieties which vegetate whence they can escape [...] That some such *process of selection* has been going on in the past seems the simplest explanation of the relatively low mortality of infectious diseases. These individuals or races of microbes which invaded the host too rapidly and caused death would be destroyed in favour of those which vegetated more slowly and in tissues permitting escape of the microbe after a certain time (1904, 825; emphasis added).

The end result of this process of adaptation or evolving parasitism, as far as health and disease are concerned, is either the establishment of a "harmless parasitism" or some disease "of little or no fatality" and a reduction of mortality through the operation of biological processes (1904, 828). The evolutionary dimension of Smith's was rapidly noted by physicians as being of "direct interest to medical men". The "law of declining virulence and advancing parasitism", for example, was discussed in relation to medicine in the editorial of *The Journal of the American Medical Association* in August 1905 (Anonymous 1905, 405). The lesson to be drawn by physicians and pathologists, according to Smith, is that infectious diseases are contingent things, that is, they "are merely epiphenomena in an evolving parasitism, by– products which tend to lessen and disappear as the parasitism approaches a biologic balance or equilibrium" (Smith 1921, 6). Accordingly, "mortality from infectious diseases would be greatly reduced through the operation of natural causes" (Smith 1904, 838). Smith was careful to emphasize, however, that "how rapidly this evolution [towards avirulence] may progress we have no means of knowing" (Smith 1921, 6).

This possibility of a natural decline in infections was obviously important to Smith as he came back to it in an address delivered a few years later entitled "The decline of infectious disease in its relation to modern medicine" (1928). He knew all too well that many factors concurred to foster the worldwide decline in infections. Considering three of them as particularly relevant, Smith discussed the "changes in economic conditions", the "application of medical science", and the "interplay of natural forces". In this last category of biological causal factors, Smith included those factors that are "largely

unknown and not controlled by human foresight" and which "tend to raise the resistance of the host and reduce the virulence of the parasite" (1928, 286).

THE LEGACY OF THE AVIRULENCE MODEL IN THE TWENTIETH CENTURY

Theobald Smith was clearly not the first bacteriologist to theorize about how virulence can either decline or increase, but he inspired generations of evolutionarily-minded scientists working in microbiology like MacFarlane Burnet, René Dubos, Frank Fenner, and others (Anderson 2004). In contrast with most of the bacteriologists and immunologists of his time, however, Theobald Smith drew more on the concepts of balance and equilibrium, than on the metaphor of the war between man and his microbial inhabitants, an attitude that reflected perhaps his overall pacifist philosophy.[105] The importance of taking into account the ecological interactions between organisms and their milieu broadly construed in order to understand disease began to be recognized in the first half of the twentieth century. Emphasizing the ecological standpoint, Burnet, for instance, argued that "there are no virulence genes as such", and that virulence should only be address "in relation to the full totality of the environment" (Burnet 1960, 1-2). This position was shared with a number of colleagues, some of whom attended the Ciba workshop on Virus, Virulence and Pathogenicity in London in 1960 mentioned previously.

In addition to bacteriology and virology, where the work of Burnet contributed to maintain its momentum, the avirulence hypothesis became entrenched within evolutionary biology itself, particularly during the coming into being of the Modern evolutionary synthesis in the 1940s and 1950s. Quoting Burnet's *Virus as Organism* the Russian geneticists Theodosius Dobzhansky – in the third edition of his *Genetics and the Origins of Species* (1951, 285) – argued that parasitic relations between host and pathogens were evolutionary unstable and "would tend to disappear and to be replaced

[105] See for instance Nicholas Kopeloff's *Man Versus Microbes* (1929). Even Burnet argued that "the general point of view which we must adopt in regard to infectious disease" is that it "is a *conflict* between man and his parasites which, in a constant environment, would tend to result in a virtual equilibrium, a climax state, in which both species would survive indefinitely" (Burnet 1953, 24; emphasis added). Smith's views on the First World War are somewhat mixed: he described the war as "the debacle of our nineteenth century civilization", accepting invitations to join the Committee on War Prohibition, on the one hand, while harbouring some pro-German sentiments, on the other (1917, in Dolman and Wolfe 2003, 427-29).

by cooperation and mutualism" (quoted in Sapp 1994, 156). Similarly, at the First symposium on host specificity among parasites of vertebrates held in Neuchâtel (Switzerland) in 1957, the German evolutionary biologist and Harvard Professor Ernst Mayr remarked, approvingly, that "many of the speakers mentioned repeatedly that there must be perfect balance between the host and the parasite. If the parasite becomes too successful it will kill the host, and if the host becomes too successful, it will eliminate the parasite" (1957, 314). Also significant is the parasitologist J.F.A. Sprent who, writing on the occasion of a centennial commemoration of Darwin's *Origin of Species*, noted that "it is widely accepted that the longer an association has been in existence in the evolutionary sense, the more likely it is to be a relationship unaccompanied by excesses on either side. Indeed, this is to be expected because associations involving damage or death, either for host or for parasite, would by natural selection eventually tend to disappear" (1962, 155). To argue for this point further, Sprent relied on Julian Huxley's book on *Evolution – the Modern Synthesis* (1942).

It is perhaps no coincidence that Sprent had referred to Huxley's book as the latter was an early advocate of this disease model, also outside strict scientific circles, for example in *The Science of Life* (1929) which he coauthored with the novelist H.G. Wells and G.P. Wells. This scholarly informed book expounded the view that not only bacteria play an important role in the "economy of nature", but that "parasitism might evolve into a symbiotic relationship that benefited both the host and parasite" (Park 2006, 502). The book was carefully read by people like Macfarlane Burnet, Frank Fenner and Joshua Lederberg. In *Biological Aspects of Infectious Disease* Burnet mentioned that his book "expresses the same general point of view that runs through Wells, Huxley and Wells' *The Science of Life*" (1940, ix quoted in Park 2006, 502), while for Lerderberg, it was "was the most influential source" of his "perspective on biology and man's place in cosmos, seen as evolutionary drama" (1993, 895). In his bestselling biography of the thyphus fever *Rats, Lice and History* (1934), Hans Zinsser also supported the thesis of his mentor and friend Theobald Smith, stating that evolution can only progress "toward a more perfect mutual tolerance between invader and invaded" (1934, 46).

During the second half of the twentieth century, the law of declining virulence and the concept of evolving parasitism also exerted far reaching, but still rather underappreciated, influence in the field of public health. Indeed, Smith's ideas about the evolution of disease by "natural forces" have informed and preceded the launching and organization of eradication programmes by the World Health Organization in the 1950s, offering indirect support to the view, (in)famously expressed by (or attributed to) the U.S. General Surgeon William Stewart in 1967, that "we can now close the book on infectious diseases". While Smith refrained from making any concrete prediction about the future of infections, others like Stewart were less careful, however. A few years before Stewart's declaration, the respected British anthropologist and epidemiologist Aidan Cockburn, who was at the time Assistant Commissioner of Health in Cincinnati (Ohio), had argued that within one hundred years most human and animal diseases could be eradicated. According to Cockburn, who referred to Smith, "we can look forward with confidence to a considerable degree of freedom from infectious diseases at a time not too far in the future". For Cockburn, "[...] it seems reasonable to anticipate that within some measurable time, such as 100 years, all the major infections will have disappeared" (1963, 150).

While this statement is often regarded by medical authorities on emerging diseases as being at best naive (Fauci 2005) Cockburn identified a crucial downside of eradicationist views for, once a disease is successfully eradicated, Cockburn wrote, "new ones will certainly appear, for we live in a world swarming with potential pathogens in many forms" (1963, 150). And yet, to those in the 1970s who voiced concerns regarding the possible resurgence of infections, Burnet responded that although in principle "there may be some wholly unexpected emergence of a new and dangerous infectious disease" we should expect "nothing of the sort that has marked the last fifty years" (Burnet and White 1972, 263). The eradication of smallpox in 1979 and the greater control over a number of other infectious diseases, including malaria, underlined these enthusiastic perspectives further ahead. Despite considerable support from several high profile scientists this evolutionary model of disease remained in search for an empirical test that would underwrite its generality and scope. The case of the myxoma virus provided such evidence.

MYXOMATOSIS: THE FIRST EXPERIMENT IN EVOLUTION

The introduction of European rabbits (*Oryctolagus cuniculus*) in Australia in 1859, coinciding with Darwin's publication of *On the Origin of Species*, was disastrous for the vegetation of the country. The situation amplified and took such dramatic proportions in the following decades that the Australian government organized a contest, promising a prize of 25 000 pounds to whoever could provide a suitable method to control the growing rabbit population. In no time Pasteur wrote a letter in a newspaper stating his intention to help Australia getting rid of the rabbits (*délapinisation*) using a biological method based on the introduction of fowl's cholera. He trusted the task of conducting the early field and laboratory experiments (and the negotiations of this project) to his nephew and assistant Adrien Loir who embarked onto his journey to Australia in February 1888. Australian authorities, however, probably skeptical to the idea of introducing foreign microorganisms into the country, declined Pasteur's help in 1889 (Chaussivert 1991).

After the Second World War the project of eradicating the rabbit populations surfaced once again. This time, a group of scientists from the Council for Scientific and Industrial Research led by the zoologist Francis Ratcliffe obtained the authorization to deploy one of the first biological weapons: the *myxoma* virus, originating from South America. Following a few unsuccessful attempts, the virus transmitted by mosquitoes spread rapidly among rabbits. It became established by December 1950 and reduced the population of 5000 individuals near Lake Urana in the Murray Valley to 50 individuals by the end of the second year (Fenner and Ratcliffe 1965). During the first two years after the inoculation, data obtained at this location revealed that the virus was 99% of the time deadly, thus supporting the view that recent associations between hosts and pathogens are more virulent than older ones. At the same location the rabbit population increased to 550 individuals during the next spring although it was subsequently reduced to 60 by December 1952, which means that the second outbreak "produced a mortality of about 90%" (Fenner 1983, 264), a noticeable difference if compared to the 99% mortality rate of the previous year. Campaigns using highly virulent strains continued after 1952.

However, the naturally selected type of strain was neither the most virulent one (grade I), nor the least ones (grade IV-V) but the "moderately virulent grade III" (Fenner 1983, 265). The explanation given of this phenomenon is that on the one hand, highly virulent strains killed rabbits too rapidly to be efficiently transmitted and propagate themselves. On the other, attenuated strains did not harm rabbits much and regressed quickly. The fact that the virus was deadly when it was released and that its virulence gradually decreased over a few years was considered by many, however, as "the best evidence supporting the generalization that disease tends to evolve toward a harmless relationship" (Bang, 1959; see also Ewald 1994, 45). Moreover, it correlates positively with the fact that myxomatosis is harmless in its South American natural host, *Sylvilagus* rabbit. Yet Fenner's conclusion was more nuanced. For him, "the co-evolution of virus and host does not necessarily lead to a situation of harmlessness' parasitism" […] "at least in the short run" (1983, 269), suggesting that given more time the myxoma virus and the Australian rabbits could evolve toward a state of commensalism. Likely, Fenner attempted to harmonize a conservative view of the evolution of virulence with the growing challenges faced by the "conventional wisdom".

CHALLENGING THE AVIRULENCE MODEL: EMPIRICAL AND THEORETICAL VIEWPOINTS

Despite the fact that Smith's hypothesis was strongly supported during the twentieth century from different perspectives, critics have been voiced against it. For instance, already in the 40s, the zoologist Gordon Ball lamented that this model, based on the observed degree of virulence, leads to incorrect phylogenies. Citing a large number of counterexamples, Ball was adamant that "one cannot maintain that relative harmlessness is *prima facie* evidence for long parasitism, and severe pathogenicity equal evidence for its relative newness" (1943, 349). He noted, elusively but correctly, that a parasite may "find aggressiveness more attractive and more valuable than an existence of peace and symbiosis" (1943, 361). Ball, however, had no alternative model of host-parasite to offer and his criticisms of the received view were largely ignored. Prior to a fuller development of the Modern evolutionary synthesis in the 60s, new work in ecology of host and pathogens in the 70s, and a global pandemic triggered by a new disease entity (AIDS), alternatives to the avirulence model were indeed hard to conceive. In reality, beyond the

persuasive rationale underlying the avirulence model, several empirical observations lent support to it, including the well-known studies on *Plasmodium falciparum* by Allison (1982) and the myxoma virus, at least initially. Today, emerging diseases – including Legionnaires' disease, Lyme disease, and pneumonia – continue to support the avirulence model as those diseases are often the result of parasites or commensal organisms which have been associated with human history over a relatively short period of time (Levin 1996).

These observations are somewhat anecdotal (*P. falciparum* aside), however, and while they seem to lend support to evolution towards harmlessness, they fail to demonstrate the converse, namely that older associations are typically avirulent (Read 1994). Besides, other empirical observations appear to plainly contradict the avirulence perspective: tuberculosis, for instance, interacts with human populations since hundreds of years and continues to be deadly. This optimistic view of the evolution of disease rapidly came under scrutiny and was challenged by the dramatic rise of emerging diseases, especially AIDS, but also dengue fever, and the evolution of antibiotic resistance in the 1970s and 1980s. Dengue fever, which has infected human populations at least since the eighteenth century, was until the 1950s followed by lifelong immunity. Yet partly as a result of the opening up of new routes of transmission for the virus and the increased mobility of human populations, the virulence of dengue fever has considerably augmented since the last fifty years, giving rise to outbreaks of dengue hemorrhagic fever and dengue shock syndrome, two previously unknown diseases (Snowden 2008, 16). The recent concept of emerging diseases (or emerging infections) reminds us that the natural world is constantly changing, although in ways that are not necessarily aligned with what our concept of human health is.[106] It is amidst this context of emerging infections, although somewhat also independent from it, that the trade-off model of virulence introduced at the beginning of this article was developed by ecologists and evolutionary biologists, and challenged the avirulence hypothesis further, and from a more theoretical angle.

[106] On the concept of emerging disease see Snowden (2008); Fauci (2005); Grmek (1993).

THE TRADE-OFF MODEL

Since pathogens have short generation timescales and exhibit sufficient genetic variation for natural selection to act, the evolution of virulence became a major topic for evolutionary ecologists in the past forty years, following the upbringing of the Modern evolutionary synthesis. The main architects of the trade-off model all had biological training in population ecology, epidemiology, or evolution, and include Sir Robert M. May, Roy Anderson (May and Anderson 1979, 1983), Simon Levin, David Pimentel (Levin and Pimentel 1981), and Paul Ewald (Ewald 1983). Developed at the end of the 1970s, this cost-benefit model explains the evolution of virulence not by a lack of adaptation, but by postulating a series of ecological compromises between the level of disease severity and a pathogen's mode of transmission, its rate of transmissibility, the speed of the host's recovery, within (and between) host selection, and so on. On this view, natural selection can foster high virulence in a system either by causing illness to the host in ways that facilitate the disease to spread, or as a consequence of maximizing transmission (Read 1994). A byproduct of a pathogen's growth, reproductive rate, and transmission (Kirchner and Roy 2002, 27), virulence results ecologically from intense host's exploitation, while from an evolutionary standpoint it is the measure of the reduction in host's fitness induced by the pathogen (Galvani 2003, 132). With the development of the trade-off model the concept of virulence became operationalized in yet another way, this time as a mathematical variable.

Importantly, the trade-off model applies primarily to pathogen's population and their evolution, not on the host, although a better understanding of changes in virulence requires considering host evolution as well (Ebert and Herre 1996). The reason for this neglect is that generation time for hosts (here, humans) is much longer and so evolution in the host population is likely to be slow. Another dimension of the model is that it does not concern itself with morbidity (at least not explicitly). Thus, symptoms like pain or injuries are not taken into account by the trade-off model and are implicitly integrated with other variables like host recovery and parasite transmission (Levins 1996). This assumption impacts on the ways in which the concept of virulence will be measured, understood, and operationalized.

The most fundamental assumption of the model is that the evolution of pathogens crucially depends on the positive coupling between transmissibility and virulence. The following, given in Levin (1996), is the equation based on which biologists can represent virulence evolution on an optimal trade-off curve:

$$R_0 = \frac{ßN}{\alpha + b + v}$$

Fig. 4 Where R_0 is the number of infections caused after a first infection and serves as a measure of Darwinian fitness; α is the level of virulence; b the rate of parasite independent-mortality; and v the rate of recovery of the host. Those variables are linked. The measure of Darwinian fitness (R_0) is directly proportional to its transmissibility (ß) at any host-density population (N) (Adapted from Levin 1996, 95).

For microparasites (bacteria, viruses, protozoa) R_0 is the basic reproductive rate of the pathogen's fitness. This coefficient refers to the average secondary infection after introduction of a pathogen in a wholly susceptible population. If R_0 – the rate of pathogen's reproduction – is greater than 1, then pathogens "can persist, maintain its population, and, as it were, emerge" (May 1993, 58). In such context there will be an observable chain of infection up to the point where there are no more hosts to infect. However, if R_0 is less than one than the infection will not be self-sustaining and will die out. If the parameters of this model were independent from each other, the equation would be compatible with the conventional wisdom. Indeed, if the degree of virulence was not connected to transmissibility (β) one would maximize R_0 by keeping α as close to 0 as possible, that is, by keeping the host alive, and this would lead to least virulent strains over time. However, when virulence is positively coupled with the mode and rate of transmission, keeping α close to 0 is not always the best (optimal) strategy for the pathogen, and therefore natural selection can maintain some level of virulence. In other words, killing the host – and increasing virulence – can be profitable for the pathogen in certain situations, but not always.

Reflecting on the case of myxomatosis, the trade-off model's theoreticians indicated that the virus did *not* actually become avirulent or harmless in the sense of Smith or Burnet. Firstly, if compared to other vectorborne diseases of humans the mortality rate of the myxoma virus was comparable with yellow fever and malaria (Ewald 1994, 45). Secondly, and more importantly, the level of virulence did not radically drop but was *stabilized* at intermediate levels because of strong selection for transmissibility (Anderson and May 1982). More recent assessments, however, indicate that the virulence has increased (Fenner and Fanitni 1999), suggesting an evolutionary arms race may be taking place between the rabbits and the virus (Sabelis and Metz 2002). Research using game theory analysis contributed to developing the trade-off model further using mathematical tools (Bremermann and Pickering 1983) and evolutionary ecologists pointed out that there are (at least) seven different possible explanations of the decrease in virulence observed in the Australian rabbit population, including the possibility that progressively acquired host resistance alone could account for the decline in mortality (Sabelis and Metz 2002).

Following the development of the trade-off model biologists continued to cling for some time onto the idea that strategies of exploitation in which the host is destroyed by the parasite cannot evolved by natural selection.[107] In fact, proponents of the avirulence hypothesis often framed their argument in terms of what is "good" for the species or the group, as Ewald remarked (1994). Acting for the good of the species (i.e. altruistically), however, amounts to subscribe to group-selectionist theories which are still problematic today. According to Ewald (1994) and others (Sober and Wilson 1999), George Williams' powerful critic of group selection in the 1960s worked as a deterrent in identifying a logical flaw in the avirulence model. Yet the controversy over whether the myxoma virus evolved by group-selection (or not) is far from being resolved as, in principle, the virus could equally have evolved through conventional individual selection (Wilson 2004), and so it seems unlikely that this element was really key in challenging the avirulence model.

[107] See Alexander (1981, 115).

CONCLUDING REMARKS

By the first half of the twentieth century, an "ecological vision" of infectious diseases was firmly established in medical laboratories across Australia and America (Anderson 2004). This ecological approach to communicable diseases grew mostly out of veterinary pathology, bacteriology, parasitology, tropical medicine, and immunology. Drawing on concepts like mutualism and competition and on inter-organismic interactions to explain epidemics in both ecological and evolutionary terms, practitioners strongly emphasized the role of the environment, natural selection, population density, and so on, to account for the changes in health and disease states. Typically, scientists attempted to develop a biologically oriented epidemiology, focusing not on the properties of the germ alone but also, and especially, on the multidimensional ecological relations between hosts and pathogens.

The main architects of the ecological vision were René Dubos, Frank MacFarlane Burnet, and Frank Fenner endorsed and promoted the avirulence hypothesis, a model of host-pathogen interactions introduced earlier by Theobald Smith which they applied in virology, microbiology, evolutionary biology, and ecology. From this perspective, the concept of virulence reflected mostly the loss of differential fitness in the host. In contrast, the mechanisms by which virulence is brought about remained a marginal focus of research. Scientists such as Dubos, Burnet and Fenner tended to characterize virulence as the result of complex biological interactions, and not just dangerous pathogenic strains. Taken together, they developed what I have called, more broadly, an *exogenous style of reasoning*. According to the thesis of the centrality of the endogenous, when constructing explanations of disease environmental factors are privileged over molecular or genetic constituents of the pathogens. The internal factors of virulence evolution (e.g. virulence genes), indeed, continue to be put largely to one side even today, as practitioners focus mostly on the selective pressures that can drive virulence upwards or downwards.

The development of the trade-off model in particular offered new insights into the evolution of and changes involved in virulence, and emphasized how crucially they depend on the route of transmission, the host's immune system, as well as on a number

of other epidemiological parameters. Building on this model experimental evidence accumulated in the 1990s (Bull 1994) and the view that pathogen and host populations always co-evolve towards a state of commensalism progressively faded away. This model rests on the view that evolution does not work for the good of the species, on the one hand, and that virulence can either increase, decrease or become stabilized at different levels, on the other (Sabelis and Metz 2002). Commensalism is no longer generally seen as the ideal and obligatory end-point of evolutionary processes. Indeed, virulence is seen as highly context-dependent, and relative to the environment and other ecological parameters (e.g. population density) that impinge on the rate at which pathogens can reproduce, transmit to other hosts, and cause disease.

To sum up, in this chapter I have explored from a *longue durée* history perspective how, in the late nineenth century, a number of issues in apparently disconnected fields such as medical bacteriology and epidemiology started to be addressed in the light of evolution, on the one hand, and how the work of Theobald Smith articulated some of these questions within the broader framework of the "law of declining virulence and advancing parasitism", on the other. Smith's experiments on cattle fever were linked further to his evolutionary views about health, disease, and host-pathogen relations. Having described the experimental basis of this model of parasitic diseases I then provided additional evidence that underlie its broad acceptance during the first half of the twentieth century and beyond. Much more remains to be said, however, about the other contributions of Theobald Smith to medicine, public health, and bacteriology.

In guise of concluding remarks, I would like to suggest that the conventional wisdom acted as a sort of "epistemological obstacle", in Gaston Bachelard's sense (1938), to the development of the trade-off model. In the early 1980s, the global phenomena of emerging diseases, the AIDS pandemic, and drug resistance have considerably weakened the idea of an obligate evolution of hosts and pathogens toward avirulence and the decline in infectious diseases, but it took a mathematical demonstration to overcome this long-held model of disease. Everyday experiences and intuition strongly testify against any reason to assume that pathogens should harm the host that supplies them with vital resources, as this would amount to a pyrrhic victory. On this view diseases are evolutionary accidents, maladapted states awaiting the operation of natural selection.

This fundamental assumption that was profoundly challenged by the mathematization of host and pathogens' relations, giving rise at the same time to a new and more flexible understanding of virulence, the outcome of which is undetermined and open to several evolutionary possibilities. And yet, the dismissal of the avirulence model as a general framework from which to look at host-pathogen interactions does not mean that the level of virulence never declines; that is, the trade-off model did not supersede or replace the avirulence hypothesis altogether in a paradigm shift type-of-way. On the contrary, and perhaps paradoxically, the development of the trade-off model broke with the previous model by circumscribing the ecological conditions under which the co-evolution toward harmlessness would be possible, and it further explained how these two competing models can perhaps even be reconciled. In effect, models that predict the evolution of intermediate levels of virulence also envisage that the relation between parasites and hosts will become less virulent over time (Lenski and May 1994). What has changed, however, is that while it was once regarded as a general model of host-pathogen interactions, the law of declining virulence turned out to be a special case of the evolution of disease.

CHAPTER 5: THE FORMATION OF THE ENDOGENOUS STYLE: THINKING ABOUT INFECTIOUS DISEASES FROM A MOLECULAR BIOLOGICAL AND BACTERIAL GENETICS VIEWPOINT

INTRODUCTION

During the first decades of the twentieth century, another style was slowly formed and eventually gave rise to a second, parallel approach to the problem of virulence and infectious diseases: the *endogenous style*. This other approach, in contrast, provided a molecular biological and bacterial genetics (and somewhat reductionist) understanding of virulence, *operationalizing* the concept from a very different viewpoint. The steps through which virulence was materialized (and operationalized) within cells and expressed by genes through other intracellular objects, like pathogenicity islands and plasmids do not form a linear, steady progression within a single discipline. As discussed in this chapter, those concepts were coined in close relation with the emergence of three disciplines in particular: molecular biology, bacterial genetics, and genomics, but also evolutionary biology. Indeed, although the endogenous style was established relatively independently of the exogenous style it obviously did not develop in isolation from the rest of the life sciences. On the contrary, the search for the minute constituents of virulence grew within the progressive establishment of what historian of science Lily Kay (1993) has called the "molecular vision" in the life sciences.

I should stress that many key actors who contributed to this other style of reasoning equally belonged, at one time or another, to the exogenous approach as defined in the introduction. This should not be surprising because one interesting aspect of styles of scientific thinking is that they can provide conceptual and practical continuity between distinct research programmes, old and new. In other words, styles can be made and remade at different places, by different, or sometimes the same people, carrying further some older ways of doing they partly inherited. For instance, before turning into an ecologically oriented biologist, Burnet had been trained in genetics of bacteriophage and

he worked for many years on virulence in microorganisms from a genetic point of view.[108] Dubos followed a similar path: first working in Oswald Avery's laboratory at the Rockefeller Institute on enzymes before turning his attention to global, ecological problems in his later writings, emphasizing the need to "think globally and act locally". And so did Lederberg who began his career working on genetic recombination in bacteria and who coined the concept of plasmid a few years later, prior to becoming one of the first scientists (trained in a molecular tradition) to ring the alarm bell on the ecological problem posed by emerging diseases in the early 1990s. Overall, one could say that there is a sense in which the exogenous style was "preformed" within the endogenous style to which it gave rise.

This chapter discusses the concept of virulence as it was developed within the endogenous style throughout the twentieth century. Looking at the distinction between pathogenic and non-pathogenic organisms, it traces how the distinction was progressively elaborated and modified according to a series of conceptual innovations which, at the same time, were permitted by technological apparartuses. After providing a brief historical overview of molecular biology this chapter focuses on the work of Fred Griffith and the role of the polysaccharide capsule as a physiological determinant of virulence in cells, and on the concept of plasmid and pathogenicity island. Emphasis is placed on how those concepts opened the door to an evolutionary understanding of virulence. In brief, both plasmids and pathogenicity islands are hypothesized as elements acquired through either endosymbiosis or lateral gene transfer. From this perspective, virulence is not the result of a lack of adaptation, but results from the rather good fit between a pathogen and its ecological niche – the host – which is being colonized thanks to some specific traits that were acquired by the organism over evolutionary time. We have seen in the previous chapter that the American bacteriologist Theobald Smith explained the decline in pathogenicity by the loss of corresponding physiological functions (even organs) on the part of the microorganisms which become progressively adapted to a particular host, having lost the occasion to exercise their pathogenic capacities. The gradual disappearance of the capacity to produce toxins is, according to Smith, an evolutionary

[108] Burnet published part of his PhD results in a paper on "Smooth-rough variation in bacteria in its relation to bacteriophage" in the *Journal of Pathology and Bacteriology* in 1929.

process which is followed by a reciprocal law-like decline in virulence and "advancing parasitism".[109] In this chapter, I describe how bacteria (and viruses) can, in contrast, be transformed into virulent, disease-causing agents by *gaining* some new intracellular and genetic material such as, for instance, a polysaccharide capsule, a large plasmid, or a pathogenicity islands. Nowadays, in the light of endosymbiosis and lateral gene transfer, microbiologists claim that we can observe "evolution in quantum leaps" (Groisman and Ochman 1996). While acquiring the capacity to cause disease thanks to new genes is a crucial aspect of how organisms become pathogens, it must not be forgotten that this capacity can occasionally also result from genomic deletion (or gene loss) (e.g. so-called "black-holes", see Maurelli 2006).[110]

In conclusion, we will see that the line between pathogenic and non-pathogenic remains blurry, despite new concepts in the life sciences that permit a better understanding of the mechanism of virulence in both bacterial and viral diseases. The separation between pathogens and commensals is often unclear: on the one hand, it is common in almost any microbial species that some members are pathogenic while others are not (Hacker and Kaper 1999), and from an ecological standpoint virulence is host-dependent and relative to a given environment, on the other.[111] For instance, pneumococci are normal inhabitants of the human respiratory tract but they can become highly pathogenic and cause severe infections (such as lobar pneumonia) if the host becomes immunocompromised. It is thus particularly important, in terms of prevention and public health measures, to understand how (and why) commensal organisms can become pathogenic or virulent or vice-versa.

[109] Bacteriologists in the first decades of the twentieth century defended this thesis which I believe was widespread. For instance, F.W. Andrews in his Presidential Address in front of the Royal Society for medicine, wrote: "the natural tendency seems to be towards loss of virulence in the absence of opportunity for its exercise, and the mechanism by which animal passage revives the power would seem to be one of natural selection in its crudest form" (1913, 4).

[110] As the number of genes in bacterial species remains roughly constant over long periods of time, it is postulated that gene gain is balanced by gene loss.

[111] Smith recognizes however that the terms virulence and pathogenicity "should be used in a comparative sense: a microbial population is more (or less) pathogenic or virulent than another population" (1978, 13/6).

WHAT MAKES AN ORGANISM A PATHOGEN?

The great majority of microbes are harmless but a fair number of them can cause severe diseases in humans, plants, and animals. Distinguishing pathogens from non-pathogenic organisms is crucial from a public health point of view. The concept of a pathogenic organism is often operationalized with reference to specific genetic or functional features. For instance, it is sometimes asserted that pathogens have "biochemical processes which set them apart from other microorganisms and determine disease production" (Smith, 1978, 13/2).[112] Since the the birth of microbiology, pathogenic organisms have been routinely identified and classified. For instance, Robert Koch discovered anthrax (1872) and the tubercle bacillus (1882) while at the same time Louis Pasteur identified fowl cholera (Brock 1990). On this view a pathogen is any member of a biological species capable of causing disease, and each disease has a specific cause. To determine the etiology of infectious diseases Robert Koch developed four theoretical postulates which must be fulfilled in order to assert that a specific pathogen is the cause of a disease. Koch's postulates (formulated by his colleague K. Loeffer) can be summarized as follows:

- a specific microorganism must always be found in the diseased tissue, cell, or organ;
- this specific microorganism must be cultivable in pure culture;
- the pure culture, when inoculated to a healthy organism, must cause the disease specifically;
- the same disease-causing microorganism can be recovered from the inoculated organism (adapted from Worboys 2007).

Koch's theoretical postulates provided a useful heuristic to link infectious diseases with identifiable causal factors, such as bacteria or parasites. In the case of tuberculosis, for instance, Koch argued that

[112] This scientist should not be confused with Theobald Smith.

> In order to prove that tuberculosis is a parasitic disease caused by the invasion of the bacilli and primarily influenced by the growth and proliferation of the latter, the bacilli had to be isolated from the body and cultivated in pure culture until devoid of all adherents products of disease originating from the animal organism; and, finally, through transfer of the isolated bacilli to animals, the same clinical picture of tuberculosis as is obtained empirically by the injection of naturally developed tuberculosis material had to be produced (Koch 1882, 861 quoted in Broadbent 2009).

But despite the theoretical appeal of the postulates, their application to concrete cases was not always possible (sometimes the organism could not be cultured; see chapter 4), and causation was also not necessarily vindicated when the postulates were fulfilled (the postulates provide a necessary, but not sufficient condition for infection to occur) (Broadbent 2009). On the *practical* side, however, Koch made a lasting contribution to microbiology and bacteriology with the invention of plate technique. Using nutrient broth mixed with gelatin Koch was able to grow and isolate pure bacterial cultures derived from a single cell on those plaques (before him, potatoes were often used as a growth medium but they were often contaminated). It is with a combination of solid culture media such as the plate technique, the theoretical postulates and a number of other sterilization and purification procedures that Koch identified causal agents of disease such as *Vibrio cholerae* (Brock 1990, 28). (Parenthetically, it is worth noting that although *Vibrio cholerae* is often taken as a typical pathogenic or virulent organism, its toxin only seriously affects humans' gut epithelium; the disease is not seen in most other animals. The virulence of *Vibrio cholerae* thus depends as much on the host's response as on the properties of the bacterium).

Historians of science often reported that following his mentor Ferdinand Cohn, Koch promoted a rigid and fixed concept of bacterial species in order to defend a doctrine of disease specificity (Smith 1932; for references see Mendelsohn 2002). In the context of his work on anthrax, for instance, Koch stated that "each disease is caused by one particular microbe – and by only one. Only an anthrax microbe can cause anthrax; only a typhoid microbe can cause typhoid" (1876, quoted in Evans 1993, 20). The adoption of a monomorphist stance was a move intended to oppose the defenders of pleomorphism (Mazumdar 1995). Indeed, accepting pleomorphism, namely the continual

(trans)mutation of one species into another – a point of view endorsed by Koch's rival, the German botanist Carl Nägeli – would prevent any rigorous and strict identification of a germ with a disease. However, an over-rigid concept of bacterial species would equally prevent both the study and the recognition of significant biological variations in bacterial cultures (Andrewes 1913). This historical claim regarding Koch's concept of species must be revised, however: recent scholarship has demonstrated that Koch's (and Pasteur's) concept of species willingly admitted *intra-species* biological variation, in particular regarding changes in virulence (Mendelsohn 2002). The disease-causing propensity – or virulence – was shown by Pasteur to have flexible boundaries and could be altered using various techniques of either attenuation or enhancement of microorganisms' pathogenic powers, for instance through serial passages of bacterial strains or by exposure to oxygen.[113]

THE ASEPSIS THESIS AND ITS CRITICS

During the late nineteenth century, although they were usually harmless, most microorganisms were considered to be, potentially at least, pathogenic, and were often even depicted as being antagonistic to mankind's health.[114] The "asepsis thesis" as Jan Sapp has called it (1994) – the claim that healthy organisms or healthy tissues are germ-free – was well-entrenched in experimental practices in bacteriological laboratories in Paris, Berlin, and London (Gradmann 2001; Cunningham 1992), and resulted in part from this belief in a clear-cut, naturl distinction between pathogen and non-pathogen. The development of Koch's postulates sharpened the dichotomy between healthy (germ-free) and diseased (presence of germ) organisms – in terms of whether an organism harbours germs or not – still further. However, problematic cases in which individuals harbouring germs without developing a disease those germs are associated with led progressively to the abandonment of this dogma during the first decades of the twentieth century, while also casting double on bacteriologists' equation that "one germ = one disease" (Strick 2000; Mendelsohn 2001). Indeed, how possibly could one hold that harbouring a germ is

[113] A detailed description of Pasteur and Koch's experiments on changes in virulence can be found in Mendelsohn (2002) and Gradmann (2009).

[114] For a recent philosophical defense of the role of microbes in human's health see Dupré (2011).

a necessary and sufficient condition for disease causation when individuals could harbour many agents classified as pathogenic without displaying any symptom?

One of the most famous cases was that of "Typhoid Mary", a nickname given to Mary Mallon (1869-1938), an American cook who between 1901 and 1907 was belived to have caused more than 25 cases of typhoid in the houses where she worked. The police arrested Mary in March 1907 upon order from the Department of Health. She was immediately taken to the bacteriological laboratory of William Hallock Park in Mannathan. The urine and feces samples were searched for traces of thyphoid and it was found that "she carried an almost pure culture of *Salmonella typhosa* in her bowels" (Strick 2000, 324). Following this investigation Park recommended adopting global measures such as pasteurization to contain infectious diseases in cases like Typhoid Mary – that is, to control asymptomatic carriers – which were surely too widespread to be controlled on an individual basis. What was needed was thus a global, even ecological, and not individual, solution. From his study of the Typhoid Mary case Park drew an important conclusion for the thesis there is an absolute distinction to be made between pathogenic and non-pathogenic organisms. The topic of asymptomatic carrier already appeard in the first edition of the microbiology textbook of another prominent bacteriologist: Edwin Oakes Jordan. From an ecological point of view, Jordan wrote, criticizing Koch's postulates, that

> The conception of a pathogenic microorganism is a relative, not an absolute one; that is to say, no microbe is known that is capable under all conditions of producing disease in all animals [...] The power of a microbe to produce morbid effects or changes depends, therefore, primarily, upon the nature of the host (1908, 11-12, quoted in Strick 2000, 32).

Drawing on the case of Typhoid Mary, Jordan continues to relativise the concept of pathogenic organism:

> Thypohoid bacillus, when swallowed by a man, can produce a serious, often mortal illness; when fed to cattle, it produces no effect. As a consequence, no sharp line can be drawn between pathogenic and non-pathogenic microorganism (Ibid.)

The thin line between pathogenic and non-pathogenic was also criticized at the turn of the past century from yet a different standpoint: the evolution of symbiosis or biological associations. In the late nineteenth century, most people had to recognize that they lived in a world swarming with microorganisms invisible to the naked eye. What is more, the great majority of these newly identified natural entities were harmless, although numerous bacteriologists wrote about the antagonistic relation between man and microbes, as mentioned above (see Kopeloff 1930). Others like microbiologist Carl Flügge, however, emphasized the role played by microorganisms in the "economy of nature" and "the existence of mankind" (1890, 5).

The study of symbiosis grew thanks in particular to the work of the Belgium naturalist Pierre van Beneden, and the French biologists Pierre Portier and Noel Bernard (Sapp 1994). These lines of research intersect with the work described previously in the ecology of virulence but they also share some epistemic affinities with the endogenous style of reasoning. Indeed, endosymbiosis – the process of integrating free-standing cellular entities such as mitochondria, plasmids, and pathogenicity islands that reproduce at the level of the whole – has recently become one of the most researched areas in the evolution of virulence (often termed "pathogenomics"), as a recent US report on *Sequence-Based Classification of Select Agents* indicates (2010). As an example of this phenomenon consider the transfer of a gene encoding a virulence factor from one species of fungi to another. Scientists located that this transfer of genetic material, which occurred in 1941, was conducive to the formation of a fungal pathogen population whose virulence was significantly enhanced and which, in turn, led to the emergence of a genuinely new disease for wheat cultures (Friesen et al. 2006). Endosymbiosis and lateral gene transfer provide incalculable opportunities for organisms to acquire new genetic material that may cause disease. This second like of criticism challenges the division between pathogenic and non-pathogenic, pathological and normal states, differently, namely by demonstrating that what was once a free-living, potentially harmful living thing could, through and by evolutionary time, become part of the normal functioning of an organism.

ON THE INTERNAL DETERMINANTS OF VIRULENCE

Today's biologists often claim that there are a number of straightforward, objective differences between commensal and pathogenic organisms: pathogens are organisms that have come to possess certain pathogenic traits, like the capacity to produce toxins or adhesins in host's cells, while commensal organisms *lack* such phenotypic traits. Virulent factors, in some cases, can be readily identified: for example the so-called virulence genes, facilitating entry into a host, multiplication within the tissues, and/or the evasion of host immunity. Pathogenic traits encoded by virulence genes are often, in turn, embedded within pathogenicity islands which are groups of genes located on the chromosomes; or alternatively, they can be located in free-replicating, mobile elements like large plasmids, or transposons. These networks form virulence regulatory systems within organisms. Harbouring (or not) one or many pathogenicity islands – sometimes forming an "archipelago" (Parsot and Sansonetti 1999) – and/or plasmids could therefore explain at a lower, and more fundamental level of biological organisation why some organisms are pathogenic while others are not.[115] Genetic and physiologic differences currently form an operational basis upon which one can distinguish between pathogens and other organisms. In other words, whilst in the ecological tradition or the exogenous style described previously virulence was operationalized in terms of unsuccessful, or incomplete, adaptation of a pathogen to its host, the functional or endogenous style described in here draws the line between virulent and avirulent organisms differently, namely by focusing on the biologic, cellular, genetic or genomic determinants of virulence.

The search and identification of the molecular basis of infectious diseases were carried on over several decades throughout the twentieth century by various practitioners, culminating with the formulation of a molecular version of Koch's postulates (Falkow 1988) and the sequencing of a large number of bacterial and viral genomes, in a search for virulence genes. Led to a large extent by microbiologists Jörg Hacker, who is head of the Center for Infectious Disease in Würtzburg (Germany), and James Kaper, the field of "pathogenomics" has emerged as the most recent (reductionist)

[115] For a contrasting view see Hacker and Carniel (2001).

approach within the endogenous style. Bacterial pathogenomics, the study of bacteria's pathogenesis is now in full swing, thanks to new genomics tools and the construction of data bases (Pallen and Wren 2007). Indeed, since the mid-90s pathogenomics seeks to use the wealth of data obtained by gene-sequence analyses to discover the genes responsible for infections in both plants and animals. Aside from coining the term "pathogenicity island", Hacker and Kaper co-edited an important book on *Pathogenicity and Other Mobile Virulence Elements* (1999).

THE EVOLUTION OF VIRULENCE AND ITS MATERIAL BASIS

According to most biologists all organisms, pathogenic or not, are the outcome of millions of years of evolution. A virulent phenotype is an evolved trait influenced by selective pressures. The capacity to cause disease is thus the result of some organisms which have evolved over long periods of time having the capacity to use other organisms (i.e. hosts) both as a source of nutrition and as a locus of reproduction and transmission; in other words, as an ecological niche. In this sense, pathogenicity ensures a selective advantage provided that the pathogen, unlike commensals, can use the host's resources without having to compete with other organisms for nutrients (Falkow 1999, xii). As Stanley Falkow puts it, the key distinction between pathogens and commensals is that "the pathogen, through evolution, has gained the inherent capacity to breach host cell barriers, while commensal species and opportunists ordinarily cannot do so" (1997, 239). Although the boundary between pathogenicity and harmlessness cannot always be sharply drawn, organisms belonging to each kind can be relatively well distinguished with respect to their evolutionary history. The challenge is then to understand the *origin* of those functional differences (Falkow 1997; Groisman and Ochman 1996).

This point illustrates how even if research within the endogenous style focused primarily on the molecular constituents of virulence there was, nevertheless, scope to address and explore *evolutionary* questions. The origins of infection mechanisms were investigated through a combination of molecular techniques and phylogenetic analyses, with the goal of unravelling the evolutionary path to acquisition of specific pathogenic features within cells and organisms. As I argue throughout this thesis the alleged rift between medicine and evolutionary thinking throughout the twentieth century is now in

the process of being bridged by experimental practices coming from several disciplines. Drawing on tools, concepts, and methods developed in bacterial genetics, biochemistry, and later molecular biology, scientists working in the endogenous style of reasoning tried primarily to establish what the material bases of virulence in infectious diseases were, and how they evolved. One of the first microbiologists to argue that virulence has an evolved material basis, or a physical component in the pathogen, was Charles Nicolle in 1939, although he did not identify any such physical structure himself. Nicolle wrote:

> We have thus good reasons to believe that virulence is linked to a *material basis*. Do not we see it sometimes undergoing rapid variations, which we can give the meaning and the name of *mutations*, and these properties being translated at the level of the organism by the acquisition of wholly new pathogenic properties regarding the animal species it infects" (1939, 66; emphasis mine).

In the making of this new research space scientists mapped out the nature and the intimate molecular mechanisms of infectious processes. In order to understand the path leading to the concept of virulent genes, pathogenicity islands, and other such new scientific objects I will briefly place the development of the endogenous style within the broader framework of molecular advances in the life sciences between 1920 and 1970.

MOLECULAR BIOLOGY AND THE FORMATION OF THE ENDOGENOUS STYLE

This section introduces some aspects of the development of molecular biology and some of its key concepts which turned out to be of central importance from an epistemological point of view in the formation of the endogenous style. Applied to bacteria and viruses this style of reasoning looks for the inner constituents of virulence and constructs explanations where the inner structures of living entities are epistemically privileged over context or environment. Historians generally disagree about how to

reconstruct the history of molecular biology but we can identify at least two schools: the structural school and the informational school (Stent 1968).[116]

The history of molecular biology has been told many times by historians, philosophers, and sociologists of science.[117] In his book on *The History of Molecular Biology* Michel Morange gives the following definition: molecular biology is "all those techniques and discoveries that make it possible to carry out molecular analyses of the most fundamental biological processes – those involved in the stability, survival, and reproduction of organisms" (1998, 1 [1994]). This "quasi-tautological" definition, as Rheinberger (2009, 7) put it, highlights the fact that molecular biology is largely (if not mostly) concerned with the coming into being of new ways of investigating (and intervening on) key organismic processes, not on the formation of a distinct field of research *per se*, although things might have been different in the early phases of the development of molecular biology, circa 1940. Nowadays, molecular biology rests primarily on the development of new techniques – or technologies –, and how these were at a later stage deployed to carry out molecular analyses of biological phenomena within other constituted fields of research across the life sciences. Morange's definition also reflects how Warren Weaver, the mathematician and then director of the natural sciences division at the Rockefeller Foundation, envisaged the new field for which he coined the term molecular biology in 1938: [118]

> Among the studies to which the [Rockefeller] Foundation is giving support is a series in a relatively new field, which may be called molecular biology, in which modern *techniques* are being used to investigate ever more minute

[116] For instance, we can also divide it up according to three phases, following molecular biologist Gunther Stent, between a "romantic phase: 1938-1952" (dominated by Max Delbrück and the seach for the material basis of heredity); a "dogmatic phase: 1953-1963" (the discovery of the double helix by Crick and Watson); and an "academic phase: from 1963" (securing the knowledge from the previous two phases) (Stent 1968, 393-394).

[117] See Rheinberger (2009; 1997); Powell et al. (2007); Strasser (2006); Burian (2005); de Chadarevian (2002); Creager (2002); Kay (2000; 1993), Morange (1998); Fox-Keller (1990); Abir-Am (1985).

[118] Also known for his collaboration with Claude Shannon on communication theory, mathematician Warren Weaver (1894-1978) is often credited for having coined the expression "molecular biology" (Rheinberger 2009).

details of certain life processes (Weaver 1970, 582, quoted in Powell et al. 2007, 11; emphasis added).

The molecular tools, concepts, and analytical procedures were mostly developed over a period of 25 years, that is, between 1940 and 1965. Once they were designed, however, scientists needed less than a decade to apply "these battery of techniques" (Burian 1993) to the whole of biology which they now pervade (Kay 1993). Accordingly, the history of molecular biology could be divided between a period of discovery, modelling, and concept-formation (1940-1965) and a period of application of these concepts, models, and techniques (1972-1980). However simplified this may be, provided that concept formation and their applications usually evolve in more continuous and intertwined ways, this framework will be useful to keep in mind. Following these "analytic" and "synthetic" phases, a third stage spanning the global, collaborative large-scale uses of molecular techniques and molecular data (so-called "data-driven" research), and the bridge with genomics, synthetic biology and systems biology, in addition to pathogenomics, could rightly be identified as a new step in the history of molecular biology. However, the formation of these new disciplines does not perfectly mirror the emergence of molecular biology itself (Morange 2009).

INSTITUTIONS, INFLUENCES, AND THREE KEY FEATURES OF MOLECULAR BIOLOGY

Molecular biology, as defined above, emerged between the 1930s and 1950s especially, from the research conducted at, and funded by, the Rockefeller Foundation and the California Technology Institute during the same period (Kay 1993). Warren Weaver, for instance, was at the Rockefeller Institute while both Max Delbrück (phage group) and Linus Pauling (X-ray crystallography; α-helix) were at Caltech, in Pasadena. Research on the operon model developed by François Jacob, Jacques Monod, and André Lwoff, however, was conducted at the Institut Pasteur in Paris. Soraya de Chadarevian (2002) studied the research effectuated in still another European institution: the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, while Angela Creager (2002) focused on Wendell Stanley's laboratory in Yale and his work on the tobacco virus. Unusually for the life sciences, the development of molecular biology was

intellectually pioneered by prominent physicists (Fox Keller 1990), including Erwin Schrödinger, Max Delbrück, Salvador Luria, Leo Szilard, and Niels Bohr, some of whom turned their attention to the life sciences in the aftermath of the Manhattan Project, particularly virology (see van Helvoort 1992) providing at the same time a strong impetus in the creation of the field of molecular biology.

In addition to Borh's lecture on "Life and Light" in 1932, Schrödinger's book *What is Life?* (1944) suggested a new "informational culture" for which the notions of code, message, and programme are indispensible (Morange 2008). When this informational language, which pervaded scientific culture and developments in computing, became sanctioned by the discovery of the double-helix and the cracking of the genetic code, the writings of Schrödinger came to be seen as having opened-up, or at least facilitated, the establishment of molecular biology from an intellectual point of view.[119] By the late 1950s the name molecular biology was in common use among biologists (Astbury 1952). The breakthrough of Watson and Crick in 1953 was possibly a "defining moment" in the history of molecular biology and the constitution of the field (Powell et al. 2007, 12), at least in retrospect. From a more institutional perspective, the creation of the *Journal of Molecular Biology* in 1959 and the awarding of the Nobel Prize to Peruz, Kendrew, Crick and Watson in 1962 cast molecular biology under a prestigious and authoritative light among other disciplines in the life sciences, even if some continued to disagree with the label.[120]

A number of characteristics of molecular biology and its influence on the life sciences as a whole are noteworthy. Firstly, this new biology opened-up a wider spectrum of possibilities to investigate life forms and their processes at the micro-level, while it emphasized at the same time the fundamental unity of all living phenomena (Kay 1993). As the Nobel Prize co-winner Jacques Monod famously said, what is true for a bacterium is equally true for an elephant. The universality of the genetic code contributed to assert

[119] Abir-Am (1985), in contrast, argued that Schrödinger was depicted as a founding father of molecular biology not because of his real influence on the formation of the field, but rather to provide some prestigious scientific roots, and thus to assert and legitimize its authority further.

[120] For instance, Conrad Waddington, the father of epigenetics, battled (without success) for the use of "ultrastructural biology" instead of molecular biology (Waddington 1961, in Powell et al. 2007, 12).

further the relatedness, from both an evolutionary and a molecular point of view, of all living and extinct forms of life.

Secondly, while working out the mechanisms, biochemical pathways, and other cycles proper to organisms, explanations of living phenomena were cast at the lowest possible level of biological organization: the molecular level. Concepts like reproduction, evolution, and growth were investigated from a bottom-up perspective. The concept of "gene" from classical genetics turned molecular and came to occupy a central epistemic place in this new biological arrangement, providing a window into both the mechanisms of hereditary changes and ontogenetic or developmental processes, although its definition remains in a state of "flux" (see Müller-Wille and Rheinberger 2009).[121] Borrowing techniques, concepts, and theories from neighbouring fields such as genetics, physiology, immunology, and microbiology, molecular biology moved away from the traditional concerns of evolutionary biology and ecology which addressed biological problems from a population and more historical perspective. This shift from whole organisms and populations to the smallest, functional constituents of living entities was not in itself new, but it indicated a radical change of scale in the life sciences. With the development of wholly new techniques, this shift was itself accompanied by a change in vocabulary to describe a number of then unknown molecular structures and, in a way, to characterize a new order of life. As Canguilhem noted in the late 60s "messages, information, programs, code, instruction, decoding: these are the new concepts of the life sciences" (1994, 316 [1968]; Stent 1968).

Thirdly, the development of those techniques marked a significant departure from biology as practiced until the 1930s. In addition to petri dishes and microscopes, molecular biology introduced new apparatus and instruments within the laboratory such as the ultracentrifuge, electron microscope, electrophoresis, isotopes, scintillation counters, and many more (Kay 1993; Rabinow 1996; Rheinberger 2010). The development of X-ray crystallography to study macromolecular structure was, however, developed in intimate relations with scientific computing methods and mathematical

[121] On the history of the concept of heredity, see Müller-Wille and Rheinberger (2007); Lopez-Beltran (2004); Gayon (2000); Jacob (1970).

models. This battery of new technological instruments changed the way biology was done in practice and brought to the fore with exceptional clarity the links between concept formation, models, and more generally, "experimental systems" (Rheinberger 1997). Science, it turns out, generalizes from locally produced knowledge in specific, practical and experimental arrangements (which can be characterized as "phenomeno-techniques") into near-universally accepted claims. Model organisms are, in this respect, tools to generate knowledge between sometimes phylogenetically distant related organisms (Ankeny and Leonelli 2011).

LIFE: FROM DECODING TO REWRITING

The first phase of molecular biology mentioned above focuses on deciphering the "book of life", to quote again Lily Kay (2000) and the processes that underlie life forms in all their diversity and functions. The second phase starting in the 1970s, however, operated differently. Above all, it dramatically shifted from an observational "understanding" of metabolic and other intra-cellular processes to one of "re-writing" life itself (Rheinberger 1995, 253). For instance, the coming into being of synthetic biology, popularized and fostered by Craig Venter is a direct attempt to build life forms from scattered bits of DNA and other macromolecules which have become available thanks to the tools of genomics and proteomics. Synthetic biology thus represents an offshoot of the latest developments of post-genomics technology in molecular biology (O'Malley 2011). Strikingly, the tools to rebuild organisms – plasmids, enzymes and so on – are themselves "parts and indeed constituents of the metabolic activities with whom, at the same time, they interfere" (Rheinberger 1995, 252). In that sense, synthetic and systems biology can be seen as the latest attempts to "naturalize" the organic world (Morange 2009, 51).

The reconstruction of the Spanish influenza virus by Jeff Taubenberger and his team (chapter 6) in Washington D.C. builds onto this second phase or rewriting in the history of molecular biology, as it continues to generate promises in terms of medical applications such as, for instance, identifying and controlling the genes for virulence in influenza virus. These attempts to reconstruct life from scratch, although they may provide a new way to

naturalize Nature, do not go about without raising some serious concerns in terms of biosecurity, however. As discussed in chapter 6 and 7, molecular pathologists drew heavily on these tools to unravel and remake the code of the virus that spurred the Spanish flu pandemic, raising questions as to whether, and to what extent, it was safe to resurrect a deadly virus that caused millions of deaths worldwide (Selgelid and Weir 2009; Aken 2007; 2006; von Bubnoff 2005; chapter 7).

Molecular biology was probably never (except at its very beginning) a unified, intended and planned project in the sense in which the Human Genome Project was. In fact, it is perhaps more akin to an "assemblage" of techniques, disciplines, objects and concepts, to speak with Rheinberger again (2009), himself referring to Paul Rabinow.[122] Today, the internal coherence of molecular biology as a discipline is sometimes questioned, partly because of the several meanings attached to the gene concept (Gayon 2007; Beurton, Falk, and Rheinberger 2000). If molecular biology is primarily characterized by a large number of specialized techniques, or by an arsenal of methods, it is striking to note that this new mode of doing biology has colonized every possible domain of the life sciences. Molecular techniques are now routinely used to investigate normal as well as pathological processes. Indeed, from the outset molecular biology's success was closely bound to the potential applications in medicine such as gene therapy, genetic testing, therapeutic (and reproductive) cloning, and stem cell research. The physical chemist Linus Pauling was the first to promote the idea of identifying and treating "molecular diseases" like sickle-cell disease (Strasser and Fantini 1998). These promises were not all fulfilled but the sequencing of the human genome, jointly announced in *Nature* and *Science* in February 2001, contributed to the revival of those possibilities and fulfilled several expectations, not least among the public. At the center of molecular biology, this newly opened space of research is the question of the structure(s) and function(s) of the gene, a problem well-known to structural chemists and geneticists. The concept of gene was often depicted as a concept that provides a "handle" on some of the most peculiar functions of organisms, including reproduction. More than just a cultural, iconic symbol exemplified in the double-helix pictogram, the gene became a

[122] Rabinow himself (2004) borrowed this term from Gilles Deleuze.

research tool in twentieth century life sciences (Moss 2003; Beurton, Falk, and Rheinberger 2000).

Another key concept whose role came into the broader picture of molecular biology only through the 1960s is the concept of plasmid, a term coined by Joshua Lederberg (1952), to designate both a symbiotic component of cells, and a heredity unit of the organism. [123] Plasmids, we now know, encode virulence genes that can be laterally transferred between bacteria. In this sense, bacterial evolution can progress in "quantum leaps", acquiring massive sets of genes that can alter virulence altogether (Groisman and Ochman 1996). The more recent field of pathogenomics turns the concept of virulence from an ecological to a molecular one, identifying "virulence factors" and trying to vindicate a molecular version of Koch's postulates. It is straightforward to conceive how this new vision of life was central to the development of the endogenous style: working within this new molecular approach, scientists set out to study how pathogens penetrate, control, or manipulate the host's defences altogether, seeking to identify which genes, or group of genes, underline these complex, systemic processes. In fact, this approach to the biologic and physical determinants of virulence cuts through many different fields and disciplines, making use of concepts and methods developed in the initial phases of molecular biology. The exogenous style is thus intimately connected to advances in molecular biology, and in systems and synthetic biology. Even if it were possible to trace the origins of this style of inquiry into the problem of infection in the last decades of the nineenth century and before, I will begin the historical and epistemological reconstruction of this style of reasoning in the late 1920s, looking first at the work of Frederick Griffith in bacteriology (1877-1941), before moving on to the discovery of the nature of DNA and plasmids, and how these new objects permitted a renewed understanding of the evolution of virulence from the 1960s until the present.

[123] For a history of the theoretical (or "quasi-epistemological") debates and laboratory practices that led to the general consensus regarding the concept of plasmid (instead of "episome") in the late 1960s see Grote (2008). See also Sapp (1994: Ch. 10), and Brock (1990: Ch. 5).

PROBING THE "SUGARCOATED MICROBE"

At a time where the term molecular biology did not yet exist, the experiments of Griffith in the late 1920s strengthened the view that virulence is typically associated with physical structures in bacteria, in particular with a polysaccharide capsule. This was a view already brought forward by Oswald Avery and his colleagues at the Rockefeller Institute in the early 1910s. Although it is unclear who first realized that a polysaccharide capsule "was a sine qua non for the virulence of the pneumococcal cell", (McCarthy 1985, 63), "by 1930 it had been established that the virulence of pneumococci was dependent on the capsular polysaccharide" (Downie 1972, 7). Evidence for the role of the sugar capsule in pathogenesis accumulated further when it was shown that pneumococci, through "bacterial dissociation", can lose their polysaccharide capsule and become avirulent.[124] The fact that unencapsulated bacteria were harmless to mice – usually fatally affected by streptococci – even when millions of them were injected into their bloodstream, strongly suggested that the capsule plays a crucial role in pathogenicity. In effect, once deprived of the polysaccharide capsule, the natural defenses of the mice were able to seek and destroy the bacteria, a process called "phagocytosis" by the Pastorian immunologist Elie Metchnikoff. Otherwise the injection of a single encapsulated pneumococcus was enough to cause rapid death in mice. Encapsulated and unencapsulated came to be associated with "smooth" (S) or "rough" (R) aspects of bacterial colonies respectively, and eventually S and R became synonymous with "virulent" and "avirulent" (McCarthy 1985, 63-65).[125] Virulence in pneumococci thus results from them having (or not) a specific physiological configuration, in this case a sugar capsule. The "sugar-coated" aspect of this microbe as Avery put it was the unmistakable sign that it was highly virulent, especially in mice but also in other animals (see McCarthy 1985). All this led Avery to conceive that by

[124] Bacterial dissociation is a process by which bacterial colonies (S or R) can transform or revert from one kind to another. This concept is linked to the debate between pleomorphism and monomorphism, and more generally to the question of variation in bacteria (Mendelsohn 2002; also Brock 1990). This adaptive process was long believed to be non-genetic, however (Hadley 1928). We now know that the incapacity of R cells in producing a capsule is linked to a mutation on a gene involved in the synthesis of the polyshaccaride capsule (Brock 1990, 224).

[125] The distinction between "rough" and "smooth" cultures was made by Arkwright (1921). See also Brock (1990, 54).

experimentally breaking down the capsule one could conceal the capacity for virulence, leading to the development of new treatments of bacterial infections.

When René Dubos visited Alexis Carrel at the Rockefeller Institute in the spring of 1927 he was introduced to Avery who was then very interested to learn that Dubos was working on soil microbiology for his doctoral dissertation at the New Jersey Agricultural Experiment Station. Dubos was then doing research on bacteria capable of decomposing cellulose – a key component of the polysaccharide capsule of pathogenic bacteria. And Avery speculated that such bacteria capable of dissolving the polysaccharide capsule could be found in soil (McCarthy 1985, 69). From then on Avery made it possible for Dubos to come to the Rockefeller Institute, and by September 1927 he became a member of Avery's lab, co-authoring several papers with Avery over the following two decades. Dubos, at a later stage, became an advocate of global and ecological approach to biological problems, coining the slogan "Think Globally, Act Locally". However, his first training was carried on in one of the most reductionist areas of microbiology where biological functions were seen as being the result of specific immunologic or chemical reactions.

CRAFTING IMMUNOLOGICAL SPECIFICITY

By the early 1910s the existence of several immunologically distinct strains of pneumococci had been demonstrated (Neufeld and Handel 1909; 1912; Avery 1915). To establish this fact, serum from infected organisms was extracted and antibodies from it were sampled. Such experiments were motivated by the possibility and the need to develop a serum to treat bacterial infections. As there were still no antibiotics available it was hypothesized that this serum could provide immunity against infectious or communicable diseases. It turned out that mice inoculated with the serum obtained by Neufeld and Handel were protected against pneumonia after injection of strains of pneumococci, although they remained susceptible to other strains. This phenomenon was analogous in its effects to the inoculation of uncapsulated bacteria in mice. Through a combination of techniques and experimental practices, the capsular material became firmly related to the virulence or avirulence of bacterial strains.

The results of Neufeld and his co-workers provided initial evidence for the existence of at least three immunologically distinct serological types (Downie 1972). In a Rockefeller monograph Avery, Chickering, Cole, and Dochez confirmed those early results. In fact, the authors identified four types of strains after the examination of cases of pneumonia: Types I, II, II, and a heterogeneous Type IV.[126] To determine the type of strain under study, the serum from infected animals, often horse, was cultivated and mixed with the type of cell used to cause the infection. As the antigen-antibody relation is specific, if the two agglutinate this means that antibodies in the sera are binding with their corresponding antigens in the bacterial strain. This serological method served as a reliable basis for the immunological specificity thesis Avery would defend over at least two decades. A few years later, Griffith (1922) obtained roughly the same classification of pneumococcal types in London as the team of Avery at the Rockefeller Institute.

When publishing his report on the observed changes in pneumococci in 1928, Griffith was investigating pneumococcal infections leading to pneumonia.[127] Griffith's experiment (below) was carried out during this period where the fixity and permanence of bacterial Types (in pneumococcus) was being established, and where the possibility for bacteria to undergo what is usually called "reversion to type" (i.e. to go from R to S or vice-versa) was highly debated. More generally, the question was whether the changes in bacterial virulence should be regarded merely as physiological adaption to a particular milieu, or whether they reflected more lasting, profound, hereditary changes (i.e. genetic mutations).[128] Although it was often pointed out that Griffith's explanation of transformation was misconceived, it is not trivial to note that his analyses of the change in serological types invoked the concept of "adaptation". Griffith's understanding rested on evolutionary (but not necessarily Lamarckian) considerations.

[126] Nowadays, more than 80 pneumococcus types are recognized (Brock 1990, 216).

[127] The clinical picture of influenza (chapter 6) results from the joint action of viral (influenza) and bacterial (pneumococcus) infections working together and producing the typical symptoms associated with the disease.

[128] The 300-page journal article of microbiologist Philip Hadley contains many useful references to this debate, in addition to a review of the evidence for and against reversion to type in bacteria (1928; see especially 212-218). For the interwar period and the revival of the debate between adaptation and selection in bacterial resistance, see Creager (2007).

To contextualize Griffith's experiment on the transforming principle accurately within bacterial genetics, some of the research by Avery conducted at the Rockefeller Institute a decade before must be retold, if only briefly. Avery is vividly remembered for his lasting contribution to the life sciences, although he began his career in medicine, and was constantly driven by the medical applications that could be derived from fundamental research in biology (Amsterdamska 1993). After more than fifteen years of experimentation with bacterial transformation, he established that the transformation of one type of pneumococcus (avirulent) into another (virulent) was the result of the action of a deoxyribonucleic acid, or DNA, and not protein (Avery, MacLoed, McCarthy 1944).[129] The isolation of "a pure gene in the form of desoxiribonucleic acid" was "an extremely exciting discovery" as Burnet once put it (1968; quoted in Downie 1972, 6). However the discovery was also indicative of still a broader shift in the life sciences. As Burnet recognized in his autobiography, the work of Avery prompted a change of direction and was a turning point in the making of molecular biology:

> in retrospect, the discovery that DNA could transfer genetic information from one type of pneumococcus to another almost brought the end of one field of scholarly investigation, medical bacteriology, and heralded the opening of molecular biology which has dominated scholarly thought in biology ever since (1968, 81, 59, quoted in Amsterdamska 1993, 5).

We can see here that not only molecular biology has made significant contributions to the development of the endogenous style, but that this style itself contributed to shape molecular biology. In particular, Oswald Avery's work was decisive in shaping the endogenous style of reasoning about virulence, as it emphasized the need to bring molecular and chemical approaches to bear on the study of infectious diseases.[130] Focusing his attention at the chemical level of explanation Avery's own experiments with

[129] On the reception of Avery's paper see Stegenga (2011) and Olby (1974).

[130] "It was largely due to his work [Avery's] that microbial parasitism evolved from an ecological concept into a body of facts and doctrines which define in physiochemical terms the mechanisms of host parasite relationships" (Dubos 1956, 41).

bacteria provided additional support to the view that distinct strains of pneumococci coexist and can be immunologically demarcated, a thesis often referred to as "immunological specificity".

The doctrine of immunological specificity was articulated by Avery, Neufeld, Handel, and Dochez in the 1910s and 1920s. Following Dubos, we can summarize it as follows:

- There exists a definite correlation between the virulence of pneumococci and their possession of a capsule detectable by microscopic and immune-chemical techniques.
- The non-capsulated variants are more rapidly killed than the capsulated forms, both *in vivo* in the normal animal, and *in vitro* in mixtures of normal serum and leucocytes. The capsule participates in virulence by increasing the resistance of the bacteria to phagocytosis.
- Encapsulated pneumococci can be separated into several different serological types by virtue of chemical differences in their capsular substances. All these are polysaccharidic in nature.
- Specific antibodies directed against the capsular polysaccharides protect against infection by neutralizing the ability of the capsules to interfere with phagocytosis (Dubos 1956, 38).

Avery's approach to changes in virulence (and its evolution) and immunological type departed considerably from ecological considerations as he focused especially on the development of cellular specialization and its role in pathogenicity. As Dubos reported, "the constant theme throughout all these interests [of Avery] was the possibility of analyzing infection *not only as an ecological phenomenon*, but also in terms of the *cellular components of the parasite* which affect the host and against which the host reacts" (Dubos 1956, 40; emphasis mine). More specifically, Avery aimed at analysing virulence separately from the host and the ecological context. According to Dubos the greatest interest in Avery's work was "the recognition that *virulence and immunity can be analysed apart from the parasite cell as a whole, in terms of some highly specialized*

cellular component" (Dubos 1956, 39; emphasis mine). Interestingly, this view was later contested by Dubos himself.

In an early paper (1915) on biological classification of pneumococci Avery emphasized that serological types are based on "well defined immunological differences" that should be taken into account in epidemiological studies. The exactitude with which the strains studied are conform to those types indicates, for Avery, "the extraordinary uniformity and comparative fixity of the specific groups" (1915, 816). Furthermore, the chemical basis of immunological specificity and the differences in antigenic properties provided not only a "reliable method" to determine the variety of bacterial strains but also "the only rational basis for the study of immunotherapy in pneumococcal infection" (Ibid.) Although this looks like a rather rigid classification, the evolutionary aspect of the origin of the immunological types was not completely left out by Avery, although it was not given full treatment either. In the concluding paragraph of a single-authored paper, Avery mused on the possibility that those types themselves have an evolutionary history. Although he refuses to provide an interpretation of those types in terms of their "phylogenetic significance" he thinks that whether the subvarieties of type II he studied are strains which have independently acquired some adaptive properties, or if they are related to "to each other and to the fixed type" by common descent "is interesting". Avery refrained from formulating "any hypothesis as to origin" (1915, 818) but he raised the question nevertheless.

A comment is in order here to clarify the significance of Avery's remarks on the concept of "type" in immunology. It is remarkable how Avery's (and other's) terminology of "fixity of type" resonates with a number of discussions that were taking place at the time outside bacteriology and immunology. Specifically, the problem of "reversion to type" was widely used and discussed in evolutionary biology and genetics. The concepts of "type" and "reversion" may at first glance appear to be rather anti-Darwinian in that they seem to caution against the existence of fixed natural types to which varieties can depart or return within some determinate limits. Nevertheless, according to Gayon "during at least fifty years, namely from 1859 (first edition of *On the Origin of Species*) until the triumph of Mendelian genetics, theoretical debates about Darwinism were marked by the ubiquitous vocabulary of 'throwback', 'return', 'reversion', 'regression',

'retrogression', and degeneration'" (Gayon, forthcoming). In brief, the concept of type was used as a basis to understand intra-species variation. Discussions concerning the nature and scope of variations in bacteria were common among bacteriologists at the time, and they were largely indebted to Darwin's work (Andrewes 1913). In immunology, however, the doctrine of specificity and type appeared to be more entrenched. The reluctance to admit changes among serological types cannot be understood without taking into account the agglutination techniques that linked specific antibodies with specific antigens. Moreover, the serum obtained from a culture would only confer protection to infections caused by the same type of strain. This thesis was to be challenged by Griffith's findings, however, leading to one of the most important discovery in the twentieth century: genes are made of DNA, not of proteins.

FRED GRIFFITH AND THE TRANSFORMING PRINCIPLE

The work of Fred Griffith (1877-1941) has not been extensively studied by either historians or philosophers of science, and in fact he remains a rather marginal figure in the history of the twentieth century life sciences.[131] Indeed, his contributions to microbiology are most of the time mentioned in passing, or merely as a prelude to the discovery that the active substance in the "transforming principle" was DNA. Born in Cheshire in 1877, Fred Griffith was an English medical bacteriologist with strong interest in public health and epidemiology. He trained in medicine in London, graduating from Liverpool University Victoria University in 1901, and then obtained a doctorate at Oxford. Firstly house-physician and house-surgeon in Liverpool he then worked as Alexander Fellow in Pathology at the Thompson Yates Laboratory. Previously, this position was occupied by his brother and the two of them carried out scientific research together under the Royal Commission on Tuberculosis, a very deadly disease in the first decades of the past century. In 1910 Griffith was appointed to the Ministry of Health as Medical Officer (Anonymous 1941, 691). His bacteriological laboratory in London was relatively small but extremely active and busy during the inter-war period. Working in close

[131] For instance, see Stegenga (2011); Amsterdamska (1993); and Lechevalier and Solotorovsky (1965). For a detailed description of Griffith's work from scientists see Brock (1990: Ch. 9); McCarthy (1985: Ch. 4); Downie (1972).

collaboration with his associate and friend William M. Scott, Griffith was a lone worker, rarely working with a research team, in contrast with other scientists like Avery. Both Griffiths and Scott died in 1941 when Griffith's London flat was bombed by the Germans (Downie 1972).

In this section I place Griffith's experiments on the transformation of serological types in bacteria within the broader context of research on the material basis of infectious diseases (particularly pneumonia), both from an epidemiological, immunological, and molecular point of view. Griffith's work was fundamental in providing a new understanding of changes in bacterial virulence and that this episode significantly contributed towards shaping the endogenous style as it singled out a particular material component for virulence phenotypes: the polysaccharide capsule.

USING BACTERIOLOGY TO ANSWER EPIDEMIOLOGICAL AND PUBLIC HEALTH QUESTIONS

In the aftermath of the influenza pandemic of 1918-19 several governmental programmes were launched both to increase surveillance of other potential pandemics, and to develop vaccines against viral and bacterial infections like pneumonia, a then-leading cause of death induced by pneumoccoci.[132] As Brock commented, this organism is a "classical example of a pathogen whose virulence is principally connected with its ability to initiate a massive invasion of vital tissues" (1990, 215).

Griffith's work on transformation in pneumococci took place in the midst of the "excitement over lobar pneumonia following the great influenza pandemic of 1918" (Brock 1990, 218). Carrying out "Pasteur's virulence-based research program" in England (Mendelsohn 2002, 29) Griffith was working on the etiology of lobar pneumonia when he made an intriguing, even startling observation that would, 16 years later, lead to the identification of DNA as the basis of the hereditary material in cells.

[132] At the time the viral nature of influenza was still unknown, and until the 30s its cause was believed to be Pfeiffer's bacillus (Smith, Andrewes, and Laidlaw 1933).

Griffith was a bacteriologist interested in immunology but his work was fundamentally driven by epidemiological considerations.[133] He was convinced that his research on pneumonia has practical applications in terms of "bacteriological diagnosis" and preparation of "antibacterial sera". However, he also thought that his analyses bore on "others issues, probably of greater importance" such as, for instance, "the occurrence and remission of epidemics", "the appearance of epidemic types in certain diseases", and the "attenuation of the infecting agents". Griffith's 1928 report on the transforming principle also sought to provide answers to different questions relative to serological types: for instance, are types only stages in the normal life-cycle of a bacterium, or are they instead the response of bacteria to changes in the host's immune system (1928, 148)? Griffith believed that answering these questions, through a close investigation of bacterial virulence in relation to variation in serological types, would greatly benefit the "epidemiology of disease" and would provide insights into "the rise and fall of epidemics". His final conclusion in the transformation paper was that the decline of epidemics among populations results not only from a decrease in the number of susceptible individuals, but also reflects also "an alteration in the character of the infective organism" (1928, 157) – hence the need to study the material and structural bases in virulence and pathogenicity to understand infective processes.

In contrast with Avery, Griffith did not hesistate to view serotypes form an evolutionary standpoint. In a paper on scarlatine epidemics, Griffith noted that "the evolution of serological types in nature is an interesting subject for speculation". For him, there was a co-evolution between humans and the scarlatine's pathogen (Streptococcus pyogenes) which was "originally much more virulent and toxigenic" but in consequence of strepctococcal infection being "more common in crowded urban communities" individuals developed a significant degree of "herd immunity". The resistance of the population, in turn, promted "the development of the multiplicity of serological races" (1933, 582). And each type exhibits a certain degree of variability, just like biological species, varieties, or races. Griffit used the language of evolutionary biologists and

[133] The medical microbiologist A.W. Downie, in the Fourth Griffith Memorial Lecture, emphasized that "Griffith's main scientific interests were related to the epidemiology of infectious disease" (1972, 2). See also Amsterdamska (1993, 30).

established a clear analogy between races in biology and the serological types in immunology. Finally, he contended that immunity was a two-way process involving hosts and pathogens: "the spread of disease in a community means ultimately not only increased resistance on the part of the host but also alteration and attenuation of the parasite" (1933, 583). There is thus, according to Griffith, an evolutionary adaptation that is being established between a human population in Britain and a pathogen which was once very virulent. Indeed, during the 1930s, most epidemics of scarlatina in Britain were caused by type I and 2, and there is "considerable evidence" that some types have caused toncilities without rashes and thus, that "types can lose their toxigenicity". Griffith concluded very much in the spirit of the avirulence model that "if the present tendency is maintained" scarlatina, eventually, "will disappear as a clinical entity" (1933, 583). A closer look at the nature of his experiment will allow for the links between bacteriological techniques and the structural basis of virulence to emerge more clearly.

GRIFFITH'S EXPERIMENT

Having contextualized the field of immunology and bacterial geneticls in the early decades of the twentieth century, we can now turn to Griffith's experiments. "In 1932 a bombshell exploded in the field of pneumococcus immunology" (Dubos 1956, 40). These words of Dubos figured in *Biographical Memoirs* on Oswald Avery and referred to Griffith's report in which the author claimed that through laboratory manipulations, bacteria can in fact change their immunological specificity, and that these changes were heritable.[134] Indeed, Griffith's serological experiments demonstrated that nonvirulent bacteria (*Pneumococci*) can be transformed into virulent types when mixed with previously heat-killed bacterial strains of a virulent type. Griffith knew that immunity can be obtained through injection of cells from sera, and that the relation between antibodies and antigens is Type-specific. (In other words, the sera obtained from an animal injected with Type II cells will be immunologically effective only against Type II cells.) When experimenting with cellular cultures he sometimes encountered some cultures displaying

[134] Note that Griffith's report was published in 1928, not 1932.

a rough aspect, however. The bacteria in those cultures were avirulent. Griffith found the following:

When he injected mice intraperitonally with a living strain of Type I, smooth (S) the animals died. When he injected living, rough-like culture (R), however, the mice lived. Similarly, when injecting mice with heat-killed Type I (S), the mice lived. However, when he injected mice with a mix of heat-killed virulent, (S), Type I pneumococci and with live, Type II non-virulent, (R) pneumococci the mice died. This was a surprising finding. Extracting serum from the blood of mice Griffith isolated strains of pneumococci Type I of S form. The bacteria had apparently changed their genetic signature in the process, that is, they reverted from Type III to Type I. These findings raised many questions and Griffith repeated his experiment a number of times with several controls each time. The explanation of this apparently strange phenomenon is that bacteria, through a form of lateral gene transfer, can pick up DNA from the environment, integrate it within their own genome, and pass down this new genetic information to the next generation. The "transforming principle" was later considered by bacterial geneticist Joshua Lederberg to be a case of "infective heredity" (Sapp 1994, 158).

Neufeld, who previously distinguished the four serological types, visited Griffith in London and was made aware of the curious results he obtained and through which experimental procedures. Once he was back in Berlin at the Koch Institute, Neufeld replicated the experiment, obtaining the same result which he published a few months only after Griffith's own paper appeared in print (Neufeld and Levinthal 1928). As soon as they received a copy of Griffith's paper Avery's team rapidly set out to replicate his experiment at the Rockefeller Institute. Avery, however, was at first very sceptical of the possibility that immunological types could undergo heritable, genetic changes. It may be that Avery's initial rejection of Griffith's findings was based on his belief that the experimental protocol was flawed. More likely, however, Avery's initial scepticism was due to the fact that he had devoted much of his professional life to developing the "doctrine of immunological specificity" (Dubos 1956, 40; Downie 1972, 3). Indeed, the results obtained by Griffith plainly contradicted the doctrine of immunological specificity Avery sought to develop over two decades of research. Once the team in Avery's lab replicated Griffith's result, however, and with other confirmations having come from

different laboratories, Avery and his colleagues embarked on a 15 year-long journey to characterize the nature of the transforming principle. This work was in a large part dedicated to understanding virulence from a chemical and molecular point of view. As Amsterdamska noted Avery's team wrote a massive report on the transforming principle and "the entire report on research on transformation is devoted to explore virulence" (1993, 33).

BACTERIAL HEREDITY: RETHINKING THE PLACE OF BACTERIOLOGY IN THE LIFE SCIENCES

The broader implications of Griffith's experiment need to be spelled out in a little more detail and placed within the wider context of the life sciences. Joshua Lederberg once used the expression "infectious heredity" – two categories usually separated in bacterial genetics and genetics during the 1940s-50s – to characterize the transmission of hereditary material in bacteria via different mechanisms such as through phage, plasmid, or other extra-chromosmal transmission. As there was no synthesis between work in bacteriology and in development or heredity during the 1920s, this connection could only be made in retrospect. In fact, according to Lederberg, Lederberg and Cavalli (1953), Griffith's own findings belong to this in-between category of being both of infectious and hereditary nature: "Infective inheritance was first described 25 years ago (Griffith 1928) (quoted in Brock 1990, 246).

The terminology deployed to assess the changes in immunological types in Griffith's experiment and elsewhere, in effect, betrays some resemblance to other (and older) experimental approaches to hereditary phenomena such as Gregor Mendel's experiments with peas. The parallel between the vocabulary and the method used by bacteriologists and the one Gregor Mendel (1822-1884) had used 50 years earlier suggests a different perspective on the significance of Griffith's experiment within the wider context of the life sciences during the interwar period. It is well-known that Mendel (1865) designed his own experimental system using peas which had either a "rough" or a "smooth" phenotypic aspect.[135] The two "characters", he showed, are heritable in a specific ratio of

[135] Instead of "smooth" one also sometimes finds the term "wrinkled" instead. On Mendel's experiment and its role in shaping the history of hereditary research see Bowler (1989).

3/1, a rate that turned out to be generalizable to a large class of organisms, and not only plants. When the ratio 3/1 was obtained, it was said that the organisms "breed true", that is, according to Mendel's "laws" of independent-assortment and segregation. It is thus interesting to note that Macfarlane Burnet, in the conclusion of an early paper on bacteriophage, observed a similarity between the R (rough) and S (smooth) variation and Mendel, and more generally between the normal and wild-type variety. Morever, he understood this difference in genetic terms such as "mutation". Burnet said: "It is probably legitimate to consider the typical S form as the normal genetically complete form and all other variants as mutations by loss of certain units comparable to the genes of Mendelian theory" (1928, 41).

Mendel's experiment consisted primarily in artificially crossing varieties of peas to determine and measure the heritability of specific phenotypic characters (i.e. smooth or rough) – an approach that led him to formulate the two laws of inheritance. Similarly, Griffith's experiment with serological types involved crossing (i.e. mixing) those immunologically distinct (segregated) types together to see whether the changes obtained could be transmitted from one generation of bacteria to the next. Griffith did not (obviously) discover a "law" of inheritance as such but he provided strong evidence that phenotypic changes in serological types (R or S) were heritable, without however being able to fully explain why this was so. (Note, however, that Mendel himself lacked a concept of hereditary unit to explain the changes he observed.) The discussion part of Griffith's 1928 report contains unexpected concepts and modes of reasoning which are more in tune with evolution, heredity and phylogeny than with bacteriology as traditionally conceived. In this sense, Griffith's experiment does not exclusively belong to epidemiology, bacteriology, or immunology, but also to genetics and perhaps even to evolution. His work was a kind of (bacterial) genetics *avant la lettre*, and it provided the impetus to research for 15 years the nature of the "transforming principle", which turned out to be, in addition, the basis of hereditary material.

Regarding changes in serological types as being not only temporary physiological adaptations to new environments but also genuine hereditary phenomena places bacteriology (and microbiology) alongside disciplines like bacterial genetics. Mendelsohn (2002, 21) has already noted that once the methods and epistemology of bacteriology are

correctly understood, a different view of the disciplines of the life sciences in the late nineenth century suddenly appears. For, according to Mendelsohn (2002), Griffith carried on to some extent Pasteur and Koch's conceptual and experimental project on virulence through the first decades of the twentieth century. It is thus not so surprising that his work also provides a different reading of the relations between disciplines in the life sciences during the interwar period.

The links between the molecular and the physiological bases of infective processes were strengthened following the characterization of the polysaccharide capsule as a "sine qua non" condition for the expression of a virulence phenotype in bacteria. The capacity of bacteria to pick up loose threads of DNA from the larger environment will allow them to acquire new infective capacities. Because of the heritable component those changes can be passed on and this new variation provides raw material on which selection can operate. Although the endogenous style leaves out selective pressures and focuses on the internal and sometimes heritable changes in virulence, it makes room for evolutionary considerations, and in particular, for understanding the path, if not the mechanism, of evolution.

What is more, the subsequent discovery that the changes in serological types were heritable brought together problems that were traditionally addressed by distinct disciplines in biology and medicine. To put it plainly, after 1944 the level of virulence in bacteria could no longer be separated from a physical, intra-cellular structure. This trend in associating the inner components of cells with virulent phenotype was amplified into a full-blown endogenous style of reasoning following the emergence of bacterial genetics and the second phase of molecular biology in the 1950s and 1960s. The development of these new practices in biology further led to the coming into being of new scientific objects and contributed overall to shaping a distinct style of reasoning in the twentieth century. I now turn to another part of this history, focusing on how plasmids, a "discursive ploy" (Sapp 1994, 160) became central in understanding the development and evolution of infectious diseases, before exploring the concept of "pathogenicity islands", as introduced in the 1980s, a few years before the rise of genomics and pathogenomics.

FROM BACTERIAL GENETICS TO GENOMICS AND PATHOGENOMICS

This section analyses the concept of "plasmid" in relation to infectious disease, and other biomedical concepts like "pathogenicity islands". Taken together, these two concepts bear directly on the problem of virulence understood from a functional and evolutionary point of view. However, as is the case in the exogenous style as defined in the present work, the ecological context (e.g. selective pressures) and more generally the environment are not the main or immediate epistemic jumping board to understanding changes in virulence, including evolutionary changes. But, as we will see, it is plain that the origin of plasmids and pathogenicity islands were considered. To understand the nature of virulence and its cause(s), research in the endogenous style places more emphasis on the internal structures of biological entities than on the larger context in which they are embedded. This seems to imply a commitment to the idea that structures are typically more explanatory than context. However, as the example of pathogenicity islands will illustrate, the hope of finding a definite structural difference between pathogenic and non-pathogenic microorganisms within their core genome is rendered problematic due to the fact that many of these structures exist in most microbial species and not just in virulent ones; these structures, however, perform different functions depending on the (ecological) context.

JOSHUA LEDERBERG'S CONCEPT OF PLASMID

The intersection of the history of plasmid research and infectious disease in the context of bacterial genetics is the focus of this section.

Lederberg was already a well-known figure in bacterial genetics by the 1950s. His early work with bacteriologist Edward Tatum in 1946 demonstrated that bacteria have genes which could be crossbred (Sapp 1994, 157). Especially because of his work on genes recombination in bacteria and on bacterial mating and evolution, Lederberg received the Nobel Prize, together with Tatum and geneticist George Beadle, in 1958. During the 1950s and 1960s, and following the work of Lederberg, three modes of gene transfer between bacteria between became known: *transformation* (DNA from one cell induces change in another one, as in Griffith's experiment); *transduction* (DNA is transmitted between

bacteria by vectors such as phages or plasmids); and *conjugation* (DNA is transmitted by cell to cell contact, a classic example of lateral gene transfer).

In his review of cytoplasmic inheritance, and amidst the proliferation of related concepts like pangenes, bioblasts, plasmagenes and proviruses, Lederberg suggested *plasmid* "as a generic term for any extra-chromosomal hereditary determinants" (1952, 403).[136] Lederberg's aim in 1952 was to reconcile, within the wider question of the scope and meaning of cytoplasmic inheritance, the conceptions of virus and plasmagenes. Discussing the concept of plasmid as a "symbiotic organism" (Ibid.), that is, as being both infectious and inheritable, he also wanted to relativise the concepts of parasitism, symbiosis and their evolution as, for him, "evolutionary pathaways are not unidirectional". Thus, he believed that to consider plasmids as viruses (or we could say, with Burnet (1946) to consider viruses as organisms) does not conflict with the idea that "a virus has become a normal constituent of the cell" (1952, 425). Indeed, plasmid can transfer virulence genes or resistance factors.

It is intriguing, however, that plasmids, through transduction, partake of the evolution of endosymbiosis – the process by which distinct biological entities (e.g. mitochondria) were integrated into today's life forms – while at the same time serving as a vector for infectious hereditary diseases. How could these extra-chomosomal elements be at the same time part of the normal genome of a microorganism *and* one of the sources of infection? This possibility should lead bacterial geneticists to reconsider theic concept of the (normal) organism and its borders, for, Lederberg asked: "if a pathogenic virus arises *de novo* tomorrow, shall we insist that the normal constituent from which it arose was not a latent virus yesterday?" (1952, 425) For Lederberg, however, this question is "almost unanswerable" because "plasmids may evolve". This concern suggests an overlap with the evolution towards avirulence as within the exogenous style. In effect, the frontier between the normal and the pathological undergoes a rectification on the basis on evolutionary novelties, such as those generated by the process of endosymbiosis, whereby what was first considered to be a pathogenic virus becomes a normal and

[136] Today, plasmids are defined as "circular DNA molecules that behave as independent genetic elements, controlling their own replication" (Brock 1990, 327).

inheritable part of an individual organism. The problem raised by the emergence of new viruses was, to be sure, one that "strains our conception of the normal" (Lederberg, Ibid.)

The questions raised by Lederberg resonate with the discussion in ecology and parasitism, and with the work of Theobald Smith and Frank Burnet. For instance, recall that Smith also wanted to consider parasitism as a "normal" phenomenon, ubiquitous in nature. Although Lederberg was acquainted with the work of Burnet he did not, however, mention the contributions of Smith or his ideas on the nature of parasitism and disease. It is only forty years later that Lederberg will bring these perspectives together in the context of emerging infectious diseases. For then, he was still working through the lens of the endogenous approach to infection and virulence, although his reflections indicate a first convergence between the two styles. According to Lederberg, the frontiers of the (normal) individual organism, *in fine*, will be delineated by pragmatic and technical considerations, however, not by definitions. Moreover, the possession of a plasmid cannot in itself serve to demarcate pathogenic from non-pathogenic organism because it is susceptible to undergo (or have underwent) evolutionary change. Nevertheless, as the next section will discuss, both the concept of plasmid and R-factors led to the development of a molecular version of Koch's postulates, and thus to such rebranding.

RESISTANCE (R) FACTORS

Although papers on the physiology of virulence appeared throughout the 1920s, it was only during the 1950s and 1960s that scientists began to establish a more direct link between physiological (phenotypic) traits, and the underlying genetic structures of bacteria or viruses (genotypes) and their evolution. The concept of plasmid, although going through a phase of eclipse between the 1950s and the late 1970s when the term "episome" was used instead (Grote 2008), was nevertheless useful to rethink the distinction between pathogenic and non-pathogenic organism.

Three classes of plasmids are noteworthy for the purpose of the present study of the material basis of virulence: The fertility (F)- factor of *E. coli*, discovered by Lederberg and William Hayes plays a role in genetic recombination; the colicin (Col)- factor, carrying genes for specific toxins; and R-factors, or resistance factors which confer drug resistance

abilities and spread widely, particularly in hospital contexts (in Grote 2008, 408). The phenomenon of drug resistance (R-factor) offered an initial link between public health concerns and the genetic basis of infection, drawing attention to the divide between the ecological and the molecular perspectives on infectious diseases. As Stanley Falkow remarks in the opening of his book on *Infectious Multiple Drug Resistance* – the first book on this topic from a molecular point of view – "it has often been a burden for the newcomer to relate the genetic, molecular, and functional properties of R-factors with their ecology and public health significance" (1975, preface).

R-factors were discovered in 1963 by Tsutomu Watanabe, a Japanese researcher, working on *Shigella bacteria* (Brock 1990, 107).[137] The species of *Shigella* bacteria was linked to phenomena of antibiotic resistance but could not be fully explained by an evolutionary or selection argument. It was observed that bacteria could lose the ability to be virulent at once, while many rounds of mutations and selection are usually required in order to evolve a mutant strain with the ability to resist drugs. Moreover, the unsual aspect of the *Shigella* strains studied by Watanabe was highlighted by the fact that some bacterial strains were sensitive to all classes of antibiotics and others to none. These phenomena did not reflect evolutionary processes, at least not the kind of processes as promoted by the Modern synthesis, i.e. mutation and natural selection. Something else was going on. The hypothesis pursued by the Japan team, and quickly experimentally confirmed, was that *Escherichia coli* present in the gut had, by conjugation (cell to cell), transferred its resistance to *Shigella* bacteria. It was concluded that due to the specific nature of the transfer (nothing else but the resistance factor was inherited) that multiple drug infection became understood as a kind of "infective heredity" (Brock 1990, 107).

Following the work of Watanabe it was known that plasmids, these self-replicating and heritable entities, play a key role in the process of virulence and resistance, for instance in *Shigella bacteria*. Led by microbiologist Philippe Sansonetti, now at Collège de France, his research team demonstrated that a large plasmid was indeed required for *Shigella* to be virulent. They were the first to devise an experimental system able to show

[137] Watanabe relates his findings not to the concept of plasmid but to "episome", a term suggested by François Jacob and Ellie Wollman. On the difference between plasmid and episome see Grote (2008).

that the possession of a large plasmid (120 kb) in *Shigella sonnei* bacteria is related to the expression of a virulent phenotype. In this case, the plasmid allows the bacteria to penetrate host's epithelial's cells. With Samuel Formal from Washington (D.C.), Sansonetti (who was then a postdoctoral researcher) confirmed this finding and using the method of bacterial conjugation he was able to transmit the plasmid to *E. coli* bacteria and even reconstruct a fully virulent *Shigella* (Sansonetti, Kopecko, and Formal 1918). Identifying the genetic profile of this pathogen, he demonstrated that without the large plasmid (form I) *Shigela. sonnei* bacteria remain non-virulent.

KOCH'S POSTULATES TURNED MOLECULAR

With the development of molecular biology techniques, such as molecular cloning (using plasmids), it became possible to target more specific (putative) genes responsible for virulence in bacteria. Microbial geneticists now routinely sequence, isolate, purify, and amplify bacterial DNA in in order to establish which gene or group of genes are involved in pathogenic processes related to infectious diseases. In other words, they want to know which genes are responsible for disease and virulence. Using contemporary molecular tools, biologists pursue, in fact, the rather old project of distinguishing between commensal organisms and pathogens from an anatomical or structural standpoint. A pathogen, from this perspective, is an organism that harbours genes which produce disease in a host. The distinction between pathogenic and non-pathogenic organisms was remade with the discovery that plasmids are key virulence factors and can also encode the so-called R-Factors. As microbiologist Stanley Falkow

> Thus, in *some but not all* strains the acquisition of these two plasmids was enough of an addition to a strain's genetic potential to tip the balance from that of a non-pathogenic commensal of the normal flora, to that of a strain now capable of producing overt disease (Falkow 1975, 253; emphasis in original).

Falkow did not completely reinvent the famous Koch's postulates – but he reformulated them in a way so as to make them applicable to genetic analysis of bacterial

virulence in the context of modern microbiology. The molecular Koch's postulates (hereafter MKP) were introduced by Falkow in a short piece that appeared in *Reviews of Infectious Diseases* (1988, 274)

- (1) The phenotype or property under investigation should be associated with pathogenic members of a genus or pathogenic strains of a species;
- (2) Specific inactivation of the gene(s) associated with the suspected virulence trait should lead to a measurable loss in pathogenicity or virulence;
- (3) Reversion or allelic replacement of the mutated gene should lead to restoration of pathogenicity;

Falkow attempted to link virulence and its measurement to the presence (or absence) of specific genes. Like for Koch, the virulent property is associated with certain members of a species and, like in nineteenth century bacteriology, the inactivation of a gene (instead of the attenuation of a germ) should lead to a decrease in virulence. Conversely, replacing a previously remove allele coding for virulence, is expected to restore infectivity. In sum, virulence genes are seen as necessary and sufficient conditions for the production of a virulent microbial phenotype. Ten years later, however, the MKP were not vindicated but challenged on the basis of genomics' new findings, chief among which is the discovery that a number of genomic regions initially thought to carry specific virulent genes are widespread across species. These genomic regions, called "pathogenicity islands" (PAIs), and as Falkow (1997) recongized, contributed to blurr the distinction between pathogens and non-pathogens further.

PATHOGENICITY ISLANDS: ECOLOGICAL SITES OF INFECTION WITHIN THE GENOME

After the discovery in the 1960s and 1970s that plasmids and phages could transmit resistance and virulence factors between bacteria and viruses, the material bases of infectious diseases were progressively elucidated. In the following decades, drawing on molecular approaches, substantial effort was devoted to understanding which region(s) in the genome is (are) associated with pathogenicity. The distinction between commensal and virulent organisms was investigated at the micro-structure level, focussing on groups

of genes potentially responsible for high disease severity. Crowning this research is the concept of "pathogenicity islands", coined by Jörg Hacker and James Kaper in the 1990s, although the work had already begun in the early 1980s with the German biologist Werner Goebel who directed the PhD thesis of Hacker.

In effect, the molecular tools developed during the "genomic" revolution have allowed the generation of extensive sets of genetic and genomic data for specific bacteria and viruses. *Haemophilus influenza* was the first bacterium to be sequenced (1995), soon followed by many others (Strauss and Falkow 1997). The Influenza Genome Sequencing Project has, as of August 2011, sequenced 7472 avian isolates which are now available in GenBank, the NIH genetic sequence database.

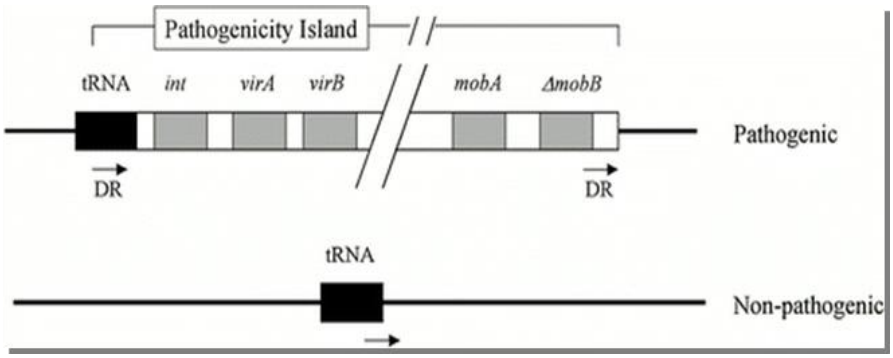

Fig. 5: a pathogenicity island. Where *tRNA* is transfer RNA; *virA* and *virB* are virulence factors; *mob* is for mobile or mobility gene; *int* is integrase gene; the thin black line represents the core genome, and genes are represented as individual gray boxes (from Hacker and Kaper 2000, 643). PAIs are genomic regions that distinguish pathogenic from non-pathogenic strains of different (or the same) bacterial species. Increasingly, however, biologists have discovered that these regions have multiple functions which are contingent on ecological context. Consequently, the term PAIs was further divided into sub-units like symbiotic islands, metabolic islands, and resistance islands (from Hentschel and Hacker 2001).

"Pathogenicity islands" (PAIs) are sequences present in genomes of prokaryotic bacteria that encode a host of virulence factors, and are often described as representing "unique genetic elements which contribute to bacterial virulence" (Hacker et al. 1997,

1089). In uropathogenic and enteropathogenic *E. coli*, for instance (where PAIs were originally investigated in the early 1980s) the virulence factors include iron-uptake systems and capsular polysaccharide (Pallen and Wren 2007). These regions code for virulence-associated proteins (Vaps) and virulence-related locus (vrl). A pathogenicity island identified in *Helicobacter pylori* Type I strain, the agent causing peptic ulcer, was found to be carrying a major virulence factor (Hacker et al. 1997).

The concept of pathogenicity islands started to be use on a large scale following the formulation of molecular Koch's postulates (Falkow 1988) and the discovery that pathogenicity islands are capable of producing evolutionary innovations in "quantum leaps" (Groisman and Ochman 1996). In effect, it was demonstrated that the integration of a PAI can, "in a single step, transform a normally benign organism into a pathogen" (Groisman and Ochman 1996, 791). However, it was only during the genomics "revolution" of the mid-1990s that the concept came into full swing, once a host of sequences became available to compare and contrast several pathogenic and non-pathogenic bacterial strains with respect to genomic regions (Hacker and Kaper 1999, 8). Most PAIs have the following features in common (Hacker and Kaper 1999, 2):

- They carry genes coding for one (or more) virulence factors (e.g. adhesins, invasions, iron uptake systems, toxins, type III and IV protein secretion systems, and so on);
- They are present within the genomes of pathogenic bacteria but are absent from non-pathogenic species or related members of the same species;
- PAIs occupy large genomic regions, that is, between 10 and 200kb, reflecting the possibility that those regions have entered the genome by lateral gene transfer;
- The DNA of PAIs is often different from that of the rest of the genome (especially in terms of guanine and cytosine (G+C) content;
- PAIs are often flanked by repeated DNA sequences which may have originated after the integration of the PAI into the genome;
- Often PAIs are made of mosaic structures and are unstable, despite being well integrated in the overall genomic environment.

It is important to note that Jörg Hacker and James Kaper pioneered the study of PAIs both from a molecular and ecological-evolutionary point of view (Hacker and Kaper 2000). They were led to this concept following the realization that specific genomic regions of pathogens carried virulence genes in ways that strongly suggested that lateral gene transfer had occurred (Hacker and Kaper 1999, 1). The discovery of PAIs in *E. coli* proved to be only the tip of the iceberg, however, as PAIs were also found in both Gram-positive and Gram-negative bacteria causing disease in humans (Hacker et al. 1997). In fact, the genomic regions called PAIs have revealed a wholly unknown set of functions which partly depend on the ecological environment.

Indeed, those coding regions initially believed to belong only to pathogenic bacterial species have turned out to be widespread among non-pathogenic species as well. To account for this finding PAIs were later renamed "genomics islands" (GEIs) and sub-divided into "ecological islands", "saphrophytic islands" and "pathogenicity islands" (or symbiosis islands) (Hentschel and Hacker 2001). According to Hacker and Kaper the underlying mechanisms in PAIs are much more common that it was first believed and can be found in very diverse phylogenetically distinct organisms. For example, *Yersinia pestis*, the agent of plague, contains a "high pathogenicity island" (HPI) coding for virulence genes (an iron uptake system) which is also be found in roughly 30% of non-pathogenic members of the species isolated from human's digestive tract (Hacker and Kaper 1999, 9). In other words, there may be pathogenicity islands hidden within the genome of non-pathogenic organisms. It seems that in nature shades of gray are more prevalent than black and white distinction, and this is especially so in the case of bacterial virulence (Wassenaar and Gaastra 2001). Does the concept of PAIs collapse in the light of this finding? Not for Hacker and Kaper, for whom the question "what is a pathogenicity island?" can be answered as follows: "a pathogenicity island is what a good microbiologist terms a pathogenicity island" (1999, 10). While this is far from satisfactory from a philosophical point of view, it may be enough in scientific contexts to know that whether the term applies (or not) is mostly a matter of interpretation and operationalization.

CONCLUDING REMARKS

At this point, there are general conclusions to be drawn from the analysis of the two styles of reasoning as detailed in chapter 4 and 5. Firstly, we can conclude that within both styles, where and how to draw a line between pathogens and commensals is not as straightforward as it may seem. When placed in a new milieu, virtually any commensal organism can become highly virulent – a point of view often expressed by most ecologically oriented biologists. In a microbiology textbook of the early twentieth century, for instance, the author expressed the following view regarding the relative capacity to cause disease:

> The conception of a pathogenic microorganism is a relative, not absolute one; that is to say, no microbe is known that is capable under all conditions of producing disease in all animals […] The power of a microbe to produce morbid effects or changes depends, therefore, primarily, upon the nature of the host […]: the typhoid bacillus, when swallowed by a man, can produce a serious, often mortal, illness; when fed to cattle, it produces no effect. *As a consequence, no sharp line can be drawn between pathogenic and non-pathogenic micro-organisms* (Jordan 1908, quoted in Strick 2000, 324; emphasis mine).

It may be the case that the author's position results from him having an "ecological" approach to infection (Strick 2000). This statement, indeed, is consistent with the views expressed by a number of scientists who have reasoned exogenously about virulence during the past century. And as we have seen, the line between virulent and avirulent is a fluid boundary at least as far as disease ecologists are concerned. One can also think of the ferocity of the myxoma virus that killed 99% of the infected rabbits in Australia upon its release in the field in the 1950s, while the same virus failed to induce disease into its natural host, the South-American rabbit.

Even from a molecular and systemic perspective provided by genomics and pathogenomics, however, the distinction between pathogenic and non-pathogenic organism, virulent and avirulent, will ultimately rest on the context in which the organism finds itself, not in the property of a gene sequence. As a recent U.S. report of the National Research Council titled "Sequence-Based Classification of Select Agents: a Brighter Line"

put it, the genomic sequence of so-called pathogenic organisms (or select agent) does not suffice to assert with certainty their pathogenicity or virulence: "Those regulatory systems are common both in pathogens and non-pathogens, so their detection by sequence analysis cannot be used as a reliable predictor of whether a microorganism is pathogenic" (National Research Council 2010, 48). Therefore, one has to look deeper into the ecological context to ascertain whether an organism is pathogenic or not, and why it is so. As to the concept of pathogenicity islands itself, it turns out that it is a sub-group of a larger category of cellular units called "genomics islands". What is more, the distinction between PAIs and other genomic island regions, when seen from an evolutionary point of view, becomes blurry. In effect, if the genomic region contributes to the microorganisms' fitness in competiting with other strains it is better called a "fitness island"; if, however, the ecological niche within which the competition takes place is the human (or animal) host, and the result is an infection, then it is appropriate to term it a pathogenicity island (Hacker and Kaper 1999, 9). "Context matters" may be a simple but telling way to express the underlying idea of a pathogenicity island.

In addition, and secondly, a number (if not most) organisms possess a number of putative virulence genes without, however, being conducive of any apparent pathology. These organisms are, in a sense, "asymptomatic carriers" of a potentially virulent disease, to borrow a term from bacteriology.[138] This problem that early bacteriologists faced is now also being addressed by molecular pathologists as well. Indeed, there is a strong conceptual continuity, in fact, between earlier views of bacteriologists such as Koch and Pasteur and the views expressed by bacterial geneticists like Falkow in the late 1980s. The formulation of the Koch postulates alone testifies of this continuity.

Thirdly, and to return to the question of operational analysis of concepts, chapter 4 and 5 illustrated how the concept of virulence was differently understood and shaped through both the "ecological vision" and the "molecular vision": the ecological style understood the concept of virulence as being the result of either a lack of adaptation to

[138] On the history of the concept of "carrier" in bacteriology see Mendelsohn (2001).

its host or a successful pathogen. In turn, the molecular style shaped the concept of virulence by insisting on its material basis within cells. However, we can notice a convergence between the styles in as much as from a bacterial genetics point of view, virulence also expresses the successful (not the lack of) adaptation of a pathogen to its host, a point Falkow made in a paper on "The microbes' view of infection" (1998). At any rate, focussing on concept formation understood as a form of scientific practice illustrated that the concept of virulence was operationalized in a variety of ways and through either environmental or large-scale approaches, or through more reductionist research programmes. As a concept in action, virulence indeed led to many developments in bacterial genetics, ecology or parasitology. Finding the explanation to the puzzling findings of Griffith necessitated undertaking a broader research approach based on the nature of virulence. In turn, this led to an even more surprising result: genes are made of DNA. As discussed in the general conclusion, the operationalisation of the concept of virulence led to the formation of several "epistemic spaces" or domains of research which, although not connected from the point of view of individual disciplines or individual researchers, are related in that they all address the problem of the nature and cause of infection which itself emerges as a central concern in biomedicine for most of the twentieth century. Wheather from the inside of from the outside, the two styles of reasoning described here can be understood as being distinct attempts to unpack a concept, or to explore a problem.

CHAPTER 6: EMERGING DISEASES AND THE 1918-19 "SPANISH" INFLUENZA PANDEMIC: ARTICULATING ECOLOGICAL AND MOLECULAR EXPLANATIONS OF VIRULENCE – WITH INSIGHTS FROM EVOLUTIONARY THEORY

INTRODUCTION

In part because "many people find it difficult to accommodate the reality that Nature is far from benign" (Lederberg 1993, 3), the generality of the "conventional wisdom" was defended far into the second half of the twentieth century.[139] In the last twenty years, however, a consensus has emerged among health scientists and physicians to the effect that the evolution of host and parasite into a commensal state is not the vanishing, obligate point it was once held to be, but is rather only one of the possible evolutionary outcomes (Anderson and May 1990). As Harvard biologist Carl Bergstrom pointed out, nowadays "we cannot count on evolution to do our work for us" (2008, 261). More generally, it is now plain that science and technology have not rid humanity of plagues and infections. This conclusion contributed in raising awareness among health professionals to what historians of medicine have called the end of an age of "hubris" (Snowden 2008). This age was characterized by a sense of effective control over most infectious diseases, thanks to the then new medical developments such as vaccines and antibiotics. Sixty years ago, it was not uncommon to read from experts on infectious diseases that fundamental research in this domain, and particularly on microorganisms, could be halted altogether. Funding further research into this area was seen as unnecessary. Frank Macfarlane Burnet, for instance, wrote in 1953 that

> Infectious diseases will always be with us, and there will always be room for further refinement in prevention and treatment; but as a major cause of death in the years of youth and maturity it is becoming relatively unimportant […] I believe that, provided the established mechanism of preventive medicine, medical care and drug production continued to function, *fundamental work on the nature of microorganisms and on the disease they produce could stop today* without influencing the current

[139] Even in the 21st century. See Dixon (2003).

> process by which all the main infectious diseases except poliomyelitis are disappearing […]It is extremely unlikely that any new principle will be needed to maintain our present very effective control of infectious disease: in that sense fundamental research is not called for by an expressed human need" (1953, 103, quoted in Fantini 1993, 454; emphasis added).

Burnet's passage asserts that infectious diseases should not be regarded as a major cause of death any more, on the one hand, and that more fundamental research in the biology of microorganisms was unnecessary, on the other. Ironically, the growing importance infectious diseases have gained in the mid-1990s turned this perspective on its head: researchers now want more studies on pathogens to be funded and fundamental research on pathogenesis, virulence factors, the ecology of host-pathogen interactions, and mobile pathogenic elements, to be carried, both for preventive and prophylactic purposes. Microorganisms, indeed, are keys to understanding and preventing epidemics and pandemics worldwide. Their potential to cause disease was long downplayed during the past century because they were seen as static, unchanging entities (Weir and Mykhaloviskiy 2010; Snowden 2008; Creager 2005).

The "very effective control of infectious disease" Burnet described, was thrown into disarray with the beginning of AIDS and other emerging infections at the turn of the 1980s such as Ebola fever, SARS, and more recently with the return of HINI influenza, thanks partly to the unimaginable capacity of microorganisms to infect and to spread. The "established mechanism of modern medicine" is no longer appropriate in term of public health response, as nosocomial infections rise and drug resistance are spreading further (see chapter 2). The end of this age of hubris epitomized here by Burnet's statement comes with the realization that infectious diseases continue to be a serious threat to human health, and that some diseases that were once believed to be eradicated could eventually return. No serious scientists today, unlike in the 1960s, would ask about and infectious disease: "does it still matter?" (Howie 1968) – even if the answer was positive.

THE 1918 INFLUENZA PANDEMIC: ECOLOGICAL AND MOLECULAR APPROACHES

Influenza pandemics are a recurrent threat worldwide, partly because of an evolutionary mechanism called antigenic *shift* that allows for distinct viral strains to combine, thereby producing a new pathogenic agent against which the body is ill-protected. Nowadays, influenza pandemics are classified as emerging and re-emerging diseases (Webby and Webster 2003), and international efforts are being made to understand why the virus achieved the exceptional virulence it did back in 1918-19. The "Spanish" influenza pandemic – one of the three influenza pandemics of the past century – is one of the deadliest events to have ever dawned of mankind (McNeill 1976). The motivation behind the global efforts to gain a better understanding of the 1918 pandemic is to draw lessons from the past in order to be better prepared for the rise of future influenza and other viral pandemics (Taubenberger 2005), an outcome predicted by influenza experts. [140] During the emergence of new pandemic ecological and molecular factors play distinct, although to some extent still poorly understood, roles. As influenza specialist Bruce Webster recently put it: "Although we know the general mechanisms by which new influenza viruses emerge, our basic knowledge of how these viruses acquire human pandemic potential is minimal, and our molecular understanding of the virus and the host factors involved in successful transmission and spread is rudimentary" (2009, 402).

In this chapter, I use the 1918-19 influenza pandemic as an example of an emerging disease to demonstrate the enduring persistence of the two distinct "styles of reasoning" or "thought-styles" in the history of virulence I developed previously (chapter 4-5). Let me briefly outline how the exogenous and the endogenous styles come into play in the present case-study. As the war was still raging at the time the 1918 pandemic broke out, explanations of the rapid changes in virulence were attributed to these uniquely detrimental environmental conditions (Oxford et al. 2002) and to humans' lack of immune responsiveness to this new infection (Kilbourne 1960; Burnet and Clarke 1942). Applying the trade-off model of the evolution of virulence to the 1918 pandemic, the

[140] The term "epidemic" refers to the occurrence of more cases than expected in a definite time period and geographical area (e.g. country); whereas pandemics are epidemics occurring over larger geographical areas, including for instance several countries (Nelson and Holmes 2004).

biologist Paul Ewald has argued that "cultural practices" (e.g. the war) lifted the obstacles that limited the evolution of virulence: the proximity of soldiers in the trenches and in the military hospitals during World War I facilitated transmission from hosts to hosts; and a high viral replication rate was favoured by natural selection which resulted in exceptionally high virulence and mortality of the pandemic (Ewald 1996; 1994; 1991). Both Ewald and Oxford stress the need to consider environmental factors in order to understand the evolution of virulence, and both recognize that part of the problem comes from the ease with which influenza viruses can mutate.

Yet, since the late 1990s, molecular pathology has provided an alternative viewpoint on the evolution of virulence in the 1918 pandemic. The identification of the viral DNA from frozen bodies and wax blocks in the U.S. and its further sequencing during the 2000s has led to a renewed emphasis on genetic and molecular determinants of the virus as being the most important cause of this dramatic event (see Holmes 2004). According to Jeffrey Taubenberger, one of the main protagonist in reviving the 1918 influenza strain, "it is possible that a mutation or reassortment occurred in the late summer of 1918, resulting in significantly enhanced virulence" (2005, 90). Indeed, Taubenberger believes that this "unique feature" of the 1918 virus – its extreme virulence – "could be revealed in his [genetic] sequence" (2005, 90). Neither of these "styles" appears to be sufficient, however, to provide a full explanation of the phenomenon. Public health workers and health scientists cannot in general make the economy of one of these approaches if they want to obtain a comprehensive picture of the many factors influencing changes in virulence during epidemics.

TOWARDS AN INTEGRATED APPROACH TO EMERGING DISEASES

Although they are often framed as alternative options to one another, these styles of explanations are not mutually exclusive. Despite the apparent divide, indeed, a recent convergence between the work of evolutionary ecologists and molecular biologists is becoming apparent. For instance, scientists attempt to "cross the line" between research on ecological contexts and selective pressures acting on host-pathogen systems, on the one hand, and the biological mechanisms of pathogens developed in response to these

pressures, on the other (Brown et al. 2006). This recent convergence in research methods results from the introduction of the concept of emerging disease which provided a platform to reframe the nature of infection, bringing together molecular and ecological approaches. Substantial political and scientific efforts were made to articulate ecological and molecular explanations as is particularly evident in the early reports and books published on emerging infections (Lederberg, Shope, and Oaks 1992; Morse 1993). A genuinely integrated approach was needed, they argued, to understand and respond adequately to the threat of emerging infectious diseases coming out of the microbial world. From its beginning in the U.S. context the concept of emerging disease was related to microbial genetics and molecular biology, while at the same time it was aligned with ecological thinking. In this respect, virulence was for the first time in the twentieth century, understood simultaneously from both an endogenous and an exogenous perspective. This broad perspective was politically and economically motivated by the consequences of the AIDS pandemic worldwide, and also by the growing recognition that infectious diseases were becoming again a major problem for public health in the West. Involving more people also meant bringing in more money. The integration of the molecular and ecological approaches was thus, in a way, a forced one.

In fact, despite the political leverage the two research styles are still disconnected to some extent as the example of the 1918 influenza pandemic, which reverberates in today's emerging infections, will show. It is not truly surprising, however, when seen in the light of the history of medicine and the life sciences in the past century, where those traditions have followed parallel and rarely intersecting routes. It would be unrealistic to expect ten or fifteen years of research to completely overturn this dynamic. Still, significant convergence in ecological and molecular research on influenza viruses can be detected, promising to bridge the gap between the endogenous and the exogenous thought-styles.

After discussing the history of the concept of emerging disease, the next two sections will examine the history of the discovery of the viral nature of influenza and the biology of the influenza pandemic. These will be followed by a section on evolutionary epidemiology and the work of Paul Ewald, one of the earliest advocates of the trade-off model (chapter 4), and then by an analysis of the work of the molecular pathologist Jeffrey Taubenberger

which will contrast the environmentally-driven style of virulence explanation with the molecular approach. Although the exogenous and endogenous styles are still very much in tension from epistemological and methodological points of view, one can see that ecologists are now working with molecular methods, and that conversely molecular pathologists are engaged in constructing complex phylogenetic networks picturing the ancestral genealogical relationship between various viral strains. This situation reflects both the use of the concept of emerging disease and also the two faces of the Darwinian explanation of organic change.

ON THE CONCEPT OF EMERGING DISEASE: HISTORICAL AND CONTEMPORARY PERSPECTIVES

The problem of *new* diseases is paradoxically an *old* one. As discussed briefly in chapter 4, *de novo* or new disease became a widely discussed topic amongst late nineteenth century's epidemiologists and physicians. In fact, the appearance of "new", previously unseen forms of pathologies (particularly epidemic diseases) has accompanied human evolution and shaped its destiny in many ways, ever since Paleolithic times (Kipple 2007). During the past two-and-a-half millennia, human populations have witnessed a number of pathologic phenomena which regularly puzzled physicians because absent from the writings of Hippocrates, Galen and other medical authorities, such as the appearance of the plague in the fourteenth century and syphilis a hundred years later. The epidemic of cholera had a similar effect in the nineteenth century Europe, and so did Athen's plague in the fourth century (B.C.) and the English sweating sickness in the eighteenth century (Grmek 1993; Temkin 1977). For, in each of these episodes just mentioned, an unrecognized disease entity came into focus, was inserted into a classificatory scheme, before vanishing and be replaced later by a new form of pathology. More recently, physicians and public health officers had to face AIDS, a disease no one had previously detected. This launched once again the discussion on the nature of new disease but this time framed as "emerging" (Snowden 2008: Cohen 2000; Grmek 1989; 1988).

This section briefly introduces and contrasts how the problem of new diseases was conceptualized in Antiquity, in the nineteenth century, and in the early twentieth century. Emphasis is placed on the historicity of the problem of new diseases and its different

interpretations before it occupied the foreground of the political arena in the mid-1990s, first in the U.S. and then across Western countries. From a *longue durée* history perspective, the epistemological shift occurring in the mid-1990s from known to unknown diseases is best understood, I argue, as one that completes a larger shift that began in the nineteenth century from a static to an evolving world.

NEW DISEASES IN ANTIQUITY: PLUTARCH'S ALTERNATIVE

The problem of new diseases was discussed by physicians during Antiquity. In the Tome V of this writings, Hippocrates, for instance, wrote that "it is certain that new diseases surface and ancient diseases go extinct" (quoted by Aglada 1869). The topic became particularly important after the unification of Mediterranean countries under the Roman Empire as new commercial routes were established between otherwise isolated lands, providing plenty of opportunities for previously isolated pathogens and "virgin" populations to come into contact. But, one may ask, are the diseases Hippocrates said they surface and go extinct genuinely new, or are they new only in the sense that they were previously undetected, or simply absent within a certain geographical area? Also, could they be explained away as biological variations of rather extreme forms of otherwise known diseases?

In parallel with the geo-political reorganisations happening in Europe in the Antiquity, especially around the Mediterranean Sea, philosophers came close to think that the problem of new diseases is by nature impossible to solve, that it is precisely an *aporie*. Philosopher and writer Plutarch (46-120 A.D.) in chapter IX of book VIII of his *Quaestiones convivales* sets himself the task "to inquire into whether it is possible that new and unknown diseases are being formed and, if so, to look for the causes of their appearance" (quoted in Mugler 1967, 15). In the opening of the dialogue Philon, one of the protagonists, engaged the debate claiming that elephantiasis is obviously a new disease as ancient doctors wrote nothing about it. This assertion was immediately countered by Plutarch himself who argued that in the *Traité des épidémies*, Athénodore reported about the occurrence of both elephantiasis (leprosy) and even hydrophobia. We are thus left, according to Plutarch, with the following alternative: either there are new diseases which are real and constitute authentically new pathological facts, or their novel character is

merely illusory and results from their having escaped physicians' attention (Plutarch, in Mulger 1967, 15). In fact, the way Plutarch framed the alternative subtly introduces a metaphysical principle. For him, indeed, the question as to whether new diseases can arise leads one to admit (or reject) a principle of change in the nature of things (Grmek 1993, 283). Following Plutarch's intervention, the other participants in the discussion agreed that the second branch of the alternative is correct, making their decision on the grounds that "with this kind of phenomenon [disease], more than anywhere else, nature is opposed to any innovation" (Plutarch, quoted in Mulger 1967, 15). Thus, new diseases could not have emerged *de novo*, but are solely the result of undetected cases. Nevertheless, Plutarch admits that new diseases can come from foreign countries, or even from outer space as Democritus himself once thought (Grmek 1993; Mulger 1967).

Renaissance physicians remained faithful to the teaching of the ancients, even when syphilis – the "French" disease – swapped Europe in the sixteenth century, bringing up the problem of new disease once again. Movements of celestial bodies and God's wrath were proposed as explanations of the new illness. However, physicians turned their attention away from these arguments and looked back into the writings of the ancients instead – Hippocrates and Galen – whose knowledge of medicine was deemed to be much superior to that of the moderns. They concluded that the disease was not genuinely new, but was possibly coming from America and resulted from a humoral imbalance (i.e. too much phlegm), suggesting either sweating or spitting as a cure to restore the balance of the body (Hays 2005, 72-73). This response of Renaissance physicians, however, ignores that Hippocrates himself believed in the possibility for new disease to be born and go extinct but it underlines the fact that the introduction of new forms of pathology in the natural world was difficult to accept.

NEW DISEASES IN THE NINETEENTH CENTURY: NATURAL HISTORY AND EXPERIMENTAL EVIDENCE

In contrast with the metaphysics of Plutarch, Renaissance physicians, and also eighteenth century nosologists who constructed rigid systems of disease classification (e.g. Boissier-de-Sauvages), nineteenth century medical doctors did not hesitate to argue for the coming into being of genuinely new diseases, and not merely previously

unrecognized cases or pathological variations. Rejecting a static and unchanging worldview as promoted by the Greeks, and the writings of the ancients, they adopted instead a more dynamic perspective on the natural world, including plants, animals, and diseases. Long before Charles Darwin, breeders had known that animals and plants could change or adapt under different local circumstances. Looking back into the history of medicine, physicians could similarly provide evidence of the sporadic appearance and disappearance of a number of diseases (e.g. plague, smallpox, scarlet fever, the English sweating sickness, and syphilis) some of which existing only in particular countries, establishing a parallel between diseases (pathology) and other (normal) forms of life.[141]

In 1836, Charles Boersch wrote an *Essai sur la mortalité à Strasbourg* [Essay on Mortality in Strasbourg] in which a large section of the book is devoted to the topic of *maladies nouvelles*. In this section, Boersch attempted to bring together animals and plants which exhibit variation and change and varieties of diseases. He wrote that

> There are animal and plant races which no longer exist in their primitive form; each day, art, education, and civilisation transform animal and plants living with us. Why would it be different in the case of diseases? Why could there not be historical diseases, just like there are fossils of plants and animal? Why, under the influence of provisional circumstances, would new and temporary disease not be born, just like new varieties of animals and plants do? This is perhaps the history of a great number of epidemics and contagions (Boersch 1836, 96 quoted in Anglada 1869, 33).

In the footsteps of newly-formed sciences such as geology and geography, and ten years after the publication of *Origin of Species*, the question of *time* began to enter mid-nineteenth century medical discourses. Some thirty years or so after Boersch, in a 600 pages volume on *Études sur les maladies éteintes et les maladies nouvelles* (1869) [Study on Extinct and New Diseases] the physician Charles Anglada stated the problem of the

[141] The French physician Charles Angalda listed a number of pathologies specific to some geographical areas: "La Plique de Pologne, le Bouton d'Alep, le Sibbens d'Ecosse, la Dadézyge de Norvège, la Lèpre d'Egypte, le Pian d'Amérique, le Yaws des côtes de Guinée, le Tara de Sibérie, le Waren de Westphalie, la Fégarite d'Espagne, le Mal de la Rose des Asturies, le Ginklose d'Islande, le Noma de Suède, la Chilolace d'Irlande" (1869, 10).

historicity of diseases as follows: “unless with side with the legend that diseases have one day befallen Earth like an avalanche, we have to acknowledge that they can only be the product [*oeuvre*] of centuries” (1869, 9). For him the existence of extinct (e.g. English sweating disease) and new diseases (e.g. cholera) is a “great fact of pathology” (1869, 1). Anglada conceptualized disease as being the result of a historical process, a development, though not yet an evolution in a Darwinian sense. This pathological development is presumably subject to natural laws, as everything else, however. Yet such laws are still to be discovered. According to Anglada, medical science has not yet been able to establish “the laws controlling the outburst of new epidemics, their momentous disappearance, their eventual returns, and their definitive extinction” (1869, 45).

Observation, according to Anglada, is the only way to understand past and present epidemics, and what it can teach us is that such banes are generally separated in space and time, and fortunately relatively rare. A full-fledged scientific explanation, in law-like terms, is however lacking, and “we are still waiting, and will probably be waiting a lot more for the Newton who will be able to calculate the evolutions [i.e. developments] of these odd meteors in the realm of pathology” (Ibid). It is plain that despite the Pastorian “revolution” in the nineteenth century no Newton of the epidemics came along, but as we have seen in chapter 2 and chapter 4 the work of Charles Darwin gave late nineteenth century physicians new conceptual tools to theorize about diseases in terms of historical change, while providing at the same time a firm basis to establish one of the most influential disease model in the twentieth century (i.e. the avirulence hypothesis) which would, however, lead to a different image of the future of infectious diseases.

Towards the end of the nineteenth century, the problem of new disease was also addressed from an *experimental* point of view. It was known that experiments on changes in virulence by serial passages in animal bodies could lead to higher or lower level of disease severity. While English epidemiologists like William Farr emphasized that a virus’s virulence, through serial passages in animals, was slowly attenuated, Pasteur pointed out that, on the contrary, serial passages *enchance* the virulence, a phenomenon he believed was linked to epidemic outbreaks and even the creation of new diseases (Moulin 1992, 290-291). Based on the belief that laboratory works translates into the natural world outside it (Latour 1983), Pasteur was inclined to think that his experiments with virus’s

virulence mimic natural process and could explain the origin of new diseases and epidemics across centuries:

> What is an inoffensive microscopic organism for humans or for a certain animal? It is a being that can develop in our body or in the body of this animal; but if this microscopic being managed to penetrate another of the thousands and thousands of *species in creation*, nothing proves that it could not invade it and make it sick. Its virulence, reinforced by successive passages through individuals of this species, could reach a level at which it could kill one or another large animal, humans or certain domestic animals. *By this method new virulences and new contagions can be created. I am inclined to believe that this is how smallpox, syphilis, plague, yellow fever appeared across the ages, and similarly that phenomena of this type explain how certain great epidemics, such as typhus for example, have appeared at one time or another* (Pasteur, Chamberland, and Roux 1881, quoted in Grmek 1995, 270; emphasis added).

NEW DISEASES IN THE EARLY TWENTIETH CENTURY: BIRTH, LIFE, AND DEATH OF INFECTIOUS DISEASES

While in the first half of the twentieth century virtually everyone in bacteriology or parasitology embraced, in one form or another, the corollary of the avirulence hypothesis, namely that infectious diseases are naturally declining (helped by modern medicine), microbiologist Charles Nicolle (1866-1936), Nobel Prize laureate in physiology and medicine in 1928, defended a different view, a view, however, very much aligned with that of his French medical predecessors in the nineteenth century, to the difference that he drew explicitly on the work of Darwin to discuss the origin of infectious diseases, both from a naturalist and an experimentalist point of view. In effect, Nicolle envisaged the unflinching dual process of upbringing and vanishing of infectious diseases – a conclusion he arrives at, paradoxically, based on the same premise as the avirulence hypothesis – namely that given enough time, infectious diseases evolve into a balance with their host: for Nicolle "infectious disease is a biological phenomenon. Bearing the characteristic of life attempting to preserve itself, it evolves and leans towards equilibrium" (Nicolle 1930, 218).

Nicolle is the author of a treatise of microbiology titled *Élements de microbiologie générale* (1901) written when he directed the Imperial Institute of Bacteriology in Constantinople. Working primarily on typhus upon his arrival in Tunisia in 1903, he identified the louse as the parasite vector of disease in man within ten years of research and was the first to use guinea pigs as experimental animals to assess the host range of the disease (Nicolle 1928). Intrigued by the impressive clinical variation in signs and symptoms among humans infected with typhus, on the one hand, and by the fact that inoculated guinea pigs sometimes failed to show signs of fever altogether, he was led to develop the concept of "inapparent infection".[142] This concept could be applied to experimental situations where the inoculated animal shows no other distinctive sign of the disease "than the virulence of the blood". With this hypothesis that infection is hidden but real Nicolle could explain why typhus could reappear on a seasonal basis, pointing to the "possible existence of inapparent forms" of the disease. Nicolle also established that inapparent infection of typhus could confer a certain degree of immune protection to the animals, as it was known in the case of man. Pioneering the field of "subpathology" he regarded in retrospect his concept of "inapparent infection" as being "without a doubt" his most important discovery (Nicolle 1928). The conceptual situation is very similar to what Theobald Smith had described in the case of Texas fever where the Southern animals showed a resistance to the parasite transmitted by the ticks (chapter 4). Indeed, Nicolle's concept means that infections are not always deadly.

Besides his scientific achievements, Charles Nicolle became mostly known for his book on *Naissance, vie et mort des maladies infectieuses* [*Birth, Life and Death of Infectious Diseases*] (1929, 129), later augmented and republished as *Le destin des maladies infectieuses* [*The Fate of Infectious Diseases*] (1939). Nicolle wrote a comment often considered as prophetic regarding to the future of novel diseases: "There will thus be new diseases. This is a critical fact. Another fact, equally critical, is that we shall only be able to identify them when they are formed, adult, so to speak. They will appear ready

[142] It would be interesting to contrast and compare Nicolle's concept of "inapparent infection" with Macfarlane Burnet's concept of "subclinical infection". But in fact, Burnet himlsef has used the concept of "inapparent infection" in the 1930s, in a paper titled on "Innaparent Virus Infections, With Special Reference to Australian Examples" (1936). See Park (2006, 513).

to strike like Minerva came out of Jupiter's brain" (1930, 129). For Nicolle, infectious diseases are being born, they develop, and they eventually die, following a pathological life cycle, so to speak. Because Nature constantly attempts to adapt microorganism to their host, and because microorganisms exhibit a great amount of biological variation, new diseases will arise although we may not be able to predict their emergence as they will appear "ready to strike". In the light of the history of the problem of new diseases this statement, however, is no more prophetic than any other similar statements made by physicians or epidemiologists before him. And yet, it *was* somehow different because it was in opposition with the idea that infectious diseases would naturally decline, on the one hand, and because after Nicolle, the age-old question of *de novo* diseases fell into oblivion for some forty or fifty years until the AIDS pandemic broke out (see Grmek 1989; 1993), on the other. This oblivion is partly linked to the neglect of the microbial world as a source of new diseases.

EMERGING DISEASE: A NEW DISEASE CATEGORY?

The early 1990s are often considered as a significant point of rupture in the international context of global public health, where the concept of "emerging" and "re-emerging" diseases have brought the problem of infectious diseases back into the foreground, where it long once stood. Historians and sociologists have characterized the period from 1992 onwards – where the concept of emerging disease was constructed and applied on a global scale – as marking a "distinctive era" in the history of public health, one where the Western world discovered that infectious diseases have not been defeated but that, on the contrary, "it [the Western world] remained painfully vulnerable and to a degree that had seemed unimaginable" (Snowden 2008, 8 and 12). For others, this period can be read off as an "epistemological break" in the field of international communicable disease, that is, a break from a world "oriented to known diseases to one responsible for a microbial world full of potential and surprise" (Weir and Mykhaloviskiy 2010, 62).

The institutionalization of the concept of emerging diseases is often credited to U.S. Institute of Medicine (IOM), and in particularly to Joshua Lederberg for whom emerging infectious disease are "clinically distinct conditions whose incidence in humans has increased" (Lederberg, Shope, Oaks 1992, 34). The expression "emerging disease" –soon

followed by “emerging infections” and “re-emerging infections” – quickly entered medical (and lay) terminology in North American and European countries. [143] In the mid-1990s the new concept replaced with two or three years the expression “communicable diseases” (Weir and Mykhaloviskiy 2010) and the century-old concept of “new” diseases (Grmek 1993). After its introduction in the U.S. context the concept of emerging disease migrated to Canada before finding its way in 1994 to the World Health Organisation in Geneva (see Weir and Mykhaloviskiy 2010). Importantly, the concept of emerging disease frames the nature of emergence not in terms of the whole being more than the sum of its parts but in terms of potentiality. Emergence is about unpredictable processes. However, one could question whether this concept was as new as Lederberg wanted us to believe it. As the previous sections illustrated, the concept of new disease was already present and discussed in the Antiquity. Moreover, Richard Krause, who was director of the National Institute of Allergy and Infectious Diseases in the early 1980s, had already predicted that infectious diseases would not decline and that new diseases may come into view. In *The Restless Tide: The Persistence Challenge of the Microbial World* (1981), Krause identified a number of causes for the rise of antibiotic resistance and infectious diseases, including changes and evolution in the genetic profile of microorganisms. Grounding his argumentation in the work of Lederberg conducted in the 1940s and 1950s in bacterial genetics and recombination, Krause put forward the view (already underlined by Lederberg) that microbes are not static entities but are “genetically flexible”, a view which was at odds with U.S. public health positions at the time (Weir and Mykhaloviskiy 2010, 32). It is only 12 years later that Lederberg would fully develop the medical consequences of his previous work, a situation that highlights the gap between public health and bacterial genetics at the time, and more generally that between the medical sciences and evolutionary biology.

Off the main scientific scene, the historian and physician Mirko Grmek suggested that the expression “new disease” – which is ambiguous – be replaced with “emerging disease” (1993). During his investigations of the AIDS pandemic Grmek noted, for instance, that the disease can be regarded both as a new and old disease: on the one

[143] See, for instance, the volume edited by Wison, Levins and Spielman (1994) on “Disease in Evolution. Global Changes and Emergence of Infectious Diseases.”

hand, AIDS is a new clinical (or nosological) entity in the sense that there was no way of conceptualizing AIDS before the elaboration of new set of concepts and tools resulting from molecular biology (e.g. study of RNA viruses); on the other hand, it is equally clear that AIDS is not "absolutely" new in the sense that the viruses responsible for AIDS did not appear ex nihilo but are derived (i.e. evolved) from biological ancestors sharing some common genetic features (Grmek 1993). Similarly, the disease known as Legionnaire's disease – that killed war veterans who gathered in a hotel in Philadelphia in 1976 – is caused by a very common bacteria which is most of the time inoffensive unless the ventilation system of the hotel allows it to spread and replicate rapidly, bringing about a highly virulent (even deadly) disease to the people who assembled there. In order to achieve some conceptual clarification, Grmek argued, in a rarely quoted-paper (in French) by disease emergentist theorists, that "to avoid misinterpretations one should substitute the ambiguous notion of 'new disease' with 'emerging disease'" (1993, 281).

Grmek further defined 5 historical situations in which a disease can be classified as emergent (1988; republished in 1993, 281)

1- It existed before it could be first identified but was overlooked from a medical point of view because it could not be conceptualized as a nosological entity;
2- It existed but was not noticed until a quantitative and/or qualitative change in its manifestation;
3- It did not exist in a particular region of the world before its introduction from other regions;
4- It never existed in a human population but only in an animal population;
5- It is completely new – the triggering germ and/or necessary environmental conditions did not exist prior to the first clinical manifestations.

The conceptual shift from "new" to "emerging" disease suggested by Grmek in 1992,[144] was greatly facilitated thanks to political and scientific leverage, for instance the publication of an influential report on *Emerging Infections: Microbial Threats to Health in*

[144] Grmek read his paper "Le concept de maladie émergente" at the International Symposium *Emerging Infectious Diseases: Historical Perspectives* held in Annecy (France), in 1992 (Grmek 1995). The paper was published one year later in *History and Philosophy of the Life Sciences* (1993).

the United States co-authored by Joshua Lederberg, Robert Shope and Stanley C. Oaks (1992). The launching of scientific journals like *Emerging Infectious Diseases* and *Ecosystem Health* around the same time also contributed to this shift (Anderson 2004), while international conferences on emerging diseases helped in bringing infectious diseases to the attention of public health officers. Particularly important were the International Symposium *Emerging Infectious Diseases: Historical Perspectives* held in Annecy (France) in 1992 and the conference on *Emerging Viruses: the Evolution of Viruses and Viral Diseases*, the latter being jointly sponsored by The National Institute of Allergy and Infectious Diseases, the Fogarty International Center of the National Institutes of Health (NIH), and the Rockefeller Foundation was held in Washington D.C. in 1989, and chaired by virologist Stephen Morse. The proceedings of the conference were later published as *Emerging Viruses* (Morse 1993).

BRINGING THE TWO STYLES OF REASONING TOGETHER

So far, chapters 4 and 5 of the thesis have dealt mostly with the problem of virulence in infectious diseases from two different perspectives – the ecological and the molecular – and it stressed how evolutionary thinking underlined and informed each of them. In this section I wish to sketch how the "ecological" and the "molecular" visions have, in the mid-1990s, started to come together, thanks to the concept of emerging disease.

From the outset, the concept of "emerging disease" was criticized in the scientific and historical literature on the grounds that it draws "disproportionate attention" from media, medical communities, policy makers, and so on to a small number of exceptional diseases such as Ebola fever or Legionnaire's disease (Woolhouse and Antia 2008). The Harvard professor Paul Farmer noted, for instance, that *emerging* diseases means nothing else than older problems appearing under new guise and not at all "emerging". For Farmer, talking about emerging disease only makes sense if one ignores the Third World altogether where most of these infections are indeed very common (Farmer 1996). It was also argued that if disease emergence is defined in terms of a steep increase of a condition over a period of time and within a defined geographical area, then the concept should embrace more than just infectious diseases and should also be applied to chronic, or degenerative diseases as well (Toma and Thiry 2003). This suggestion goes hand in

hand with the recognition that a number of chronic diseases like cervical cancer and peptic ulcers have a viral origin, blurring the distinction between infectious and chronic diseases (Gold 1998). In spite of these limitations and some potential biases, the concept of emerging disease is now widely in use and we must ask what use it is good for.

One of the things that made the concept of emerging disease appealing was the fact that it is an "active concept", to use the words of sociologists Weir and Mykhaloviskiy (2010). It is such, in their views, because the concept has "provoked far-reaching legal, political, and technical transformations in international communicable disease control" (2010, 30). Their approach supports what I have called in the introduction an analysis of "concepts in action". The idea is that although they may seem so, concepts are not inoccuous and can have powerful effects on various aspects of society. To understand concepts in action one thus has to look at the changes triggered by the introduction of a new concept in one or more scientific, social, ethical, or legal domains, and how the concept was later reshaped in the light of those transformations. But the concept of emerging disease did something else for the field of public health and medicine: it permitted to bring together two research traditions in the field of infectious disease that were previously disconnected, constituting isolated styles of reasoning. In other words, the concept of emerging disease not only rebranded infectious diseases in economic and political terms; it also opened-up a conceptual space to reconcile the molecular and ecological aspects of infection and virulence that were yet isolated. Bacterial genetics and microbiology were immediately brought to bear on the concept of emerging disease. However, ecological aspects of the problem were empahsized strongly in two of the most influential and fundamental texts that propelled the concept into the global arena, triggering, in return, a number of institutional changes.

In the preface of his book on *Emerging Viruses*, Stephen More provided a vivid picture of the integrated approach that was needed in order to deal with emerging infections

> In attacking the problem of emerging viruses, scientific knowledge of the agent is essential, and the recent flowering of molecular biology and molecular genetics has provided powerful tools for analyzing and tracking

> viruses, and is yielding fresh insights into viral evolution. But viruses are of necessity dependent on their hosts, requiring us to have an appreciation of the factors that may influence the interaction of a virus with a host. Although many of these factors are molecular or cellular, when the host is human, social factors can play a very significant role in both dissemination and expression of disease. On a larger scale, many epidemics can be understood only in their ecological context (Morse 1993, viii).

Similar considerations were voiced by Lederberg and Shope in their report (1992). They remarked that emerging diseases results mostly from anthropocentric reasons than for changes in the biology of the viruses or bacteria causing diseases:

> In discussions about the emergence of "new" diseases, considerable debate has centered on the relative importance of de novo evolution of agents versus the transfer of existing agents to new host populations (so-called microbial traffic). It is sometimes presumed that the appearance of a novel, disease-causing microorganism results from a change in its genetic properties. This is sometimes the case, but there are many instances in which emergence are due to changes in the environment or in human ecology. In fact, environmental changes probably account for most emerging diseases.

Weir and Mykhaloviskiy (2010) do recognize that both scientists have from the outset argued that an integrated approach is needed. My argument is that this decision has a deeper historical signification because it crystalized two thought-styles that were previously divided for most of the twentieth century. The concept of plasmid coined by Lederberg (1952) provided public health medicine with a powerful tool to investigate the emergence of new diseases. The lateral (or horizontal) transfer of plasmids between bacteria, often containing several virulence factors, can give rise to new genetic combination able to infect humans and animals. And yet, this concept appeared in a research tradition (or style) where the focus was primarily on the biological mechanisms of bacteria (or viruses), not on the broader environmental context, or on the medical significance of these findings. Similarly, the epidemiologists Robert May and Roy Anderson, among others, constructed a new model of virulence evolution in the late 1970s that can explain why in some ecological contexts, virulence can decrease, increase

or become stabilized. While the conceptual and modelling tools existed to explain, and possibly limit, the spread of infectious diseases worldwide, those two styles remained apart until the mid-1990s. I now turn to the history of the Spanish influenza pandemic of 1918, an emerging and re-emerging disease whose exceptional virulence continues to puzzle scientists.

THE SPANISH INFLUENZA PANDEMIC – AN EMERGING AND RE-EMERGING DISEASE

The emergence of the (misnamed) "Spanish" influenza pandemic of 1918-19 is the first of the three major influenza pandemics that occurred during the past century – and is regarded as one of the most devastating episodes in medical history. Once described as "the biggest unsolved problem of theoretical epidemiology and public health practice" (Burnet and Clark 1942), the consequences of this dramatic event rendered many wary about the emergence of future respiratory disease pandemics (Webby and Webster 2003).

The name "Spanish" flu comes from the fact that Spain was neutral country during World War I, providing at the same time a scapegoat to take the blame for this calamity (Philipps and Killingray 2003, 7). In fact, it is only in Spain that the publication of medical reports on influenza was authorized during the war and as a consequence, it got blamed for the pandemic and was considered responsible for it. One of the first papers to appear in London *Times* (June 1918) was titled "The Spanish Influenza – a sufferer's symptoms" (in Johnson 2006, 37). Using a concept coined by Grmek (1969), it could be said that the 1918 influenza pandemic has ruptured the fragile "pathocenotic equilibrium" prevailing during the first decades of the twentieth century, creating at the same time a new ecological order among diseases on a global level.[145]

[145] Grmek defines the concept of pathocenosis as the "equilibrium in the frequency of all the diseases affecting a population". This frequency "conforms to certain rules" and can be "studied using mathematical models" (1990, 156-8). Grmek famously applied this concept to explain the emergence of the AIDS pandemic (1990; 1989) and other emerging pathogens (1993; 1995; 1969). For a recent article on the influence of one disease on another see Noymer (2010) who argues that the 1918 pandemic was a significant factor in the decline of tuberculosis in the early decades of the twentieth century as it killed many individuals infected with T.B.

In addition to the 1918 famous Spanish influenza pandemic, two other influenza pandemics occurred in the following decades, one in 1957-58 ("Asian" influenza, H2N2) and the other in 1968 ("Hong Kong" influenza, H3N2). In comparison to the Spanish flu pandemic, the last two major pandemics were more benign, the former causing between 1.5 and 2 million deaths, and the latter, one million. The recent H5N1 pandemic caused a few deaths only between 1997 and 2004 (Taubenberger 2005, 87). Despite the (crucial) fact that antibiotics were available during the second two pandemics, this raises the question: why was the 1918 pandemic so deadly?

A significant amount of research in virology, parasitology, and more recently evolutionary biology has grown since the 1930s, attempting to explain the exceptional virulence of the 1918 pandemics. Very often the question is framed as follow: is the biological nature of the virus the key to explain the pandemic, or is the explanation of such unprecedented virulence more likely to be found in the equally exceptional (environmental, social, political, nutritional, and so on) conditions of the pandemic? Endogenous and exogenous thought-styles remain divided on this issue, and researchers (continue to) ignore each other's work, as explanations are often polarized regarding the cause of the pandemic. Most of the time, only one of the above situations is cast as the sufficient (and the right) explanation of the emergence of the pandemic, while minimal attention is paid to other explanatory schemes. However, such complex phenomenon is unlikely to be explained by a single-sided approach. I believe these two perspectives can be combined, or integrated, in order to provide a deeper and better understanding of the situation, and perhaps contributing in avoiding another such devastating phenomenon. In fact, the epistemological and ontological complexity of a situation like this one requires a pluralistic, integrative explanatory framework that is able to bring together and make sense of the relations between the biological, the social, and even the political dimensions at stake.

OPERATIONALIZING THE VIRAL NATURE OF INFLUENZA

From the early 1890s to the early 1920s the cause of influenza was believed to be a bacterium: *Bacillus Influenzae*, also named Pfeiffer's bacillus after the work of the German bacteriologist (a colleague of Koch) and physician Richard Pfeiffer (1858-1945)

who isolated the microorganism in 1892 from patients displaying flu symptoms.[146] Even in the late 1930s, when convincing evidence (provided by Smith, Andrewes and Laidlaw in 1933) demonstrated that influenza was not caused by a bacterium but by a virus, historians and bacteriologists continued to credit him with the discovery, and regarded his views on the status of influenza as largely correct and well established (see for instance Bulloch 1979, 390 [1938]). For instance, in his *Textbook of bacteriology* (1919) Hans Zinsser wrote that "the relationship between the clinical disease known as influenza or grippe and the Pfeiffer's bacillus has been definitely established by numerous investigations" (1919, 540; quoted in Johnson 2006, 22). The bacteria held responsible for influenza, however, proved difficult to culture and it was not found in all patients diagnosed with influenza (Epps 2006). The idea that the causal agent of influenza was a bacterium remained long entrenched amongst bacteriologists, bacteria being identified as the cause of a number of diseases affecting humans such as anthrax, cholera and plague. This can be seen as a lasting effect of the influence of the "bacteriological paradigm" on influenza research during the first half of the twentieth century (van Helvoort 1993).

In 1918, at a "Discussion" on influenza organized by the Royal Society of Medicine, the Chief Medical Officer Sir Arthur Newsholme summarized the situation concerning the nature of influenza and its cause(s) as follows:

> The first difficulty is to define Influenza. Is it one disease or a group of diseases? And is the disease now prevailing the disease which prevailed in the spring? […] These two questions cannot easily be separated. […] There can be no doubt that all these bacteria, often acting in conspiracy, have contributed greatly to the recent mortality from influenza, but whether there is in addition a hitherto undiscovered virus to which influenza is primarily due is still a moot point (1918, 1-2; quoted in Johnson 2006, 20).

An important argument against the bacterial nature of influenza emerged from a series of experiments conducted in the early 1920s by Peter Olitsky and Frederic Gates, two American researchers at the Rockefeller Institute who provided a useful operational definition of the disease. In a string of papers (1921a; b; c; d; e; f) the authors

[146] Pfeiffer was at the time the head of a research Institute for Infectious Diseases in Berlin.

demonstrated that the “active substance” or the “active agent” they isolated could pass through the membrane of the filter Berkefeld (V and N). Moreover, this active agent could cause the same influenza symptoms in rabbits and guinea pigs inoculated with unfiltered material. Importantly, it could also survive immersion in glycerol for up to nine months (1921, 371). Given that the membrane of the filter stops bacteria while allowing viruses and smaller organisms to get through, this suggested to Olitsky and Gates that they were handling an organism of a different nature without, however, drawing the conclusion that it was a virus.

Another crucial step in the discovery of the viral nature of influenza came from a series of experiments with swine. In 1918, 1928 and 1929, epidemics of what seemed to be a disease of influenza were observed among pigs in Iowa, in the USA. The symptoms of this disease in pigs were so similar to human influenza that it was named “swine influenza”. Swine influenza was recognized as a clinical entity as early as 1918 (Koen 1919). The relatedness of the two disease and the fact that it emerged shortly after the Spanish flu pandemic led some to believe that the virus spread from humans to swine in the fall of 1918; however, there is no conclusive evidence of such a jump yet (Taubenberger 2006, 94).

Despite these researches on swine influenza and the work of Olitsky and Gates, the nature of influenza’s causative agent remained somewhat mysterious throughout the 1920s. For a decade or so, scientists obtained mixed results when trying to discover and identify the agent of swine influenza. Reproducing results obtained by other research groups proved to be a complicated task sometimes. For instance, in a paper published in 1920¸ Murray described swine influenza as resulting from a small Gram-negative coccus which (he thought) he had successfully inoculated to healthy swine. Others, however, failed to obtain the same coccus described by Murray in their cultures; they observed, rather, two types of organisms, none of which being able to produce the disease when inoculated nasally to swine, however (McBryde, Niles and Moskey 1928). The breakthrough came towards the end of the 1920s with the work of American bacteriologists Richard Shope and Paul Lewis.

Working on “hog” cholera, Shope and Lewis investigated the two devastating epidemics affecting swine that occurred in the autumn of 1928 and 1929 in Iowa. In a series of experiments described in three articles they demonstrated that swine influenza was not caused by *Hemophilius influenza suis* (or Pfeiffer’s bacterium) but by a virus. *H. influenzae suis*, however, was always found in animals who suffered from influenza. In the first paper (Shope 1931), Shope describes how he inoculated swine influenza intranasally to healthy animals using 8 strains taken from Iowa during the epizootic episode of 1928. “The experimental disease has the same feature as the epizootic” (1931, 358) although he observed variation among individuals regarding severity and mortality. The nature of the agent inducing swine influenza was still debated, however, partly because the agent held responsible for the disease sometimes failed to produce symptoms among healthy hogs.

In the second paper (Lewis and Shope 1931), the authors reported their observations on the characters of the organism believed to cause the disease, or at least accompanying it. “The suspected organism was very similar to, if not identical with, *H. influenzae*” in terms of morphology and other characters (1931, 362-64). For instance, the cultures of biological samples taken to be infected with swine cholera revealed the presence of “thin, curved bacilli which varied considerably in length”. Moreover, this organism was found in the respiratory tracts of all experimental animals and those suffering from spontaneous influenza attacks. The authors suggested the name *Hemophilius influenzae suis* for this organism or swine origin (1931, 364). Although “there is no real basis” for differentiating between *H. influenza suis* and *H. influenza* the two organisms differ serologically and pathologically. What is more, however, *H. influenza suis* alone was unable to induce disease in animals in which it was inoculated. Out of 13 swine that were inoculated intranasally, *H. influenza suis* held no pathogenic effect on 11 of them (1931, 370). The other two who fell ill had mistakenly received a mixture of *H. influenza suis* and the “filtrate agent” (i.e. the virus).

In the third paper Shope (1931b) gives an account of the symptomatic differences between animal diagnosed with swine influenza and those he inoculated with the filtrate disease. The disease induced by the “filtrate agent”, that is, the agent that resulted from the filtrating process, “was definitely not typical swine influenza” (1931b, 374). In all cases it was “much milder than swine influenza”; there was no elevation of temperature

generally; some apathy was observable in addition to diminution in appetite; slight cough was also noticed. Yet, "the extreme prostration so common in swine influenza infections was not seen" (Ibid). The filtrate disease was, however, infectious and could be easily inoculated either intranasally or by contact.

Importantly, in animals diagnosed with swine influenza, *H. influenza suis* was always found in the respiratory tracts but it was never found in animals inoculated with the filtrate disease alone (1931b, 375). Shope hypothesised correctly that "the combination of the organism and the filterable agent may be essential for the production of the natural disease" (Ibid.) He established this fact with the help of some more experimental animals inoculated with a mixture of *H. influenza suis* and the filtrate disease. Following this experiment, "a disease typical of swine influenza in all clinical and pathological respects and indistinguishable from that induced by unfiltered infectious material resulted in all instances" (1931b, 381). He concluded that swine influenza is due to the action of the filterable virus and *H. influenza suis* "acting together". Their mode of action can either be that the virus creates an entry point for the bacterium to infect the host and determine the clinical picture of the disease; or that the virus is the most important vector in causing the disease, *H. influenza suis* only making things worse, so to speak. In other words, Shope demonstrated that the filtrate agent was a necessary but not sufficient condition to produce swine influenza. In his conclusion, he ventured the possible explanation that a similar dual-process could be at work in the case of human influenza: "a careful investigation would seem warranted of the possibility that Pfeiffer's bacillus and a filtrable agent act in concert to cause influenza in man" (Shope 1931b, 384).

The isolation of the actual causal agent of human influenza was made in the early 1930s by a group of three British virologists working at the National Institute for Medical Research: Wilson Smith, C.H. Andrewes and P.P. Laidlaw. An epidemic of influenza at the beginning of the year 1933 provided them with ample material to study the disease experimentally. Their paper "A Virus obtained from Influenza Patients" was published in *Lancet* in July 1933. Building on the work of Shope and Lewis they provided conclusive evidence regarding the viral nature of influenza in humans. Using lung materials from deceased cases and throat gargling from suspected cases of influenza Wilson, Laidlaw and Andrewes attempted to inoculate mice, guinea pigs, monkeys, hamsters and rabbits

without much success, however. Intracerebral, intratesticular and intraperitoneal attempts to inoculate these animals with infectious material were tried in turn but also in vain. Wilson then decided to use ferrets as experimental organism.[147] At the time, this animal was being used in his institute by his colleagues Laidlaw and Dunkin. It was also known that ferrets were highly susceptible to distemper, a virus affecting dogs (Burnet and White 1972, 208). Wilson also decided to inoculate the animals intranasally. Using throat-washings from C.H. Andrews who was ill, he inoculated two ferrets with influenza in February 1933. In his notebook he wrote "Ferret 1 looks somewhat seedy – crusts round nose and slight discharge with suggestion of pus – eyes also watery – sneezing". A month later or so Wilson fell ill too – it is believed he catched it from a ferret! Collecting his own gargling he used it to inoculate ferrets with what became known as the Wilson Smith or WS strain (on this see Eden 1966, 482).

This initial success set the stage for further research by the three co-workers, leading to the identification of the virus of influenza in humans. Using ferrets as experimental organisms they inoculated them with throat-washings obtained from patients who displayed influenza symptoms. These samples were filtrated and the filtrates were then inoculated, both subcutaneously and intranasally to ferrets. The animals soon became ill, showing influenza symptoms (1933, 66). Reasoning along the lines of Shope and Lewis, the authors asserted that "epidemic influenza in man is caused primarily by a virus infection" (1933, 68). Macfarlane Burnet and White observed that this paper opened up a new "epoch in the study of influenza" making it available to "experimental study"; influenza was "no longer a nebulous entity" (1972, 208).

Research on influenza was facilitated by changing the "experimental animal", that is, by switching from ferrets to mice. The latter was easier to standardize and also cheaper to obtain. Although it was not readily susceptible to the virus, experimenters could transfer the virus rapidly from individual to individual, artificially selecting the most virulent ones causing deadly pneumonia. The next technique in line was the use of chicken eggs to grow and culture the virus. The "egg technique", developed by Burnet, provided an ideal environment for the virus to develop rendering influenza one of the

[147] On the distinction between experimental organism and model organism see Ankeny and Leonelli (2011).

easiest viruses to grow and study artificially for a period of ten to fifteen years (Burnet and White 1972). As Burian emphasized many years ago, it is important for scientists to have "the right organism for the right job" (1993).

THE BIOLOGY OF INFLUENZA

In a sense influenza cannot be regarded as a "single disease" entity (Johnson 2006, 10). Indeed, the family tree of influenza viruses contains two genera: one that includes influenza A and B viruses and the other influenza C viruses, and the two genera are distinct in terms of host range and virulence factors. Type A is the most common of all, and can infect a wide range of hosts, including, pigs, horses, seals, whales and birds. This type of virus is also the most redoubtable as it has the potential to cause pandemics. Type B is believed to infect only humans (especially young children) and Type C (another genus) can infect both humans and swine (Johnson 2006, 10).

Influenza viruses are enveloped negative strand RNA viruses and belong to the genus *Orthomyxoviridae* (Taubenberger 2005). The virus of the Spanish flu pandemic belongs to the type A influenza, known as H1N1. Influenza A and B viruses contain eight discrete gene segments, coding for at least one protein. The surface of influenza A viruses are covered by three types of proteins hemagglutinin (HA), neuraminidases (NA) and matrix 2 (M2). The structural configuration of HA proteins is that of a triangular spike. These spikes allow the virus to bind to both host cells and red blood cells, causing the latter to agglutinate (whence the name hem*agglutinin*), facilitating entrance into the host, and triggering infection. Once the infection is over, antibodies responding to hemagglutinin spikes are formed, allowing the immune system to recognize the signature of the viral strain in case of another infection episode. Neuraminidases (NA) are instead shaped like small mushrooms. They also form spikes on the surface coat of the virus but the function of NA is to cleave glycoproteins into two so as to facilitate the propagation of the virus from cell to cell. It opens-up cells for infection. Antiviral drugs target NA in order to block their exit, and antibodies to NA are also produced after the infection.

Influenza A viruses are further subdivided by serological types, which is the genetic characterization of the surface glycoproteins HA and NA. There are 16 HA and 9 NA

proteins known as of today. These surface glycoproteins define the virus's identity in terms of what the immune system detects and attacks. The different major families of flu are combinations of the two, hence the designation “H5N1” for the recent threat. The 1918 virus was H1N1. The “offspring” of the Spanish flu pandemic viral strain were replaced in 1957 by the H2N2 subtype. This one circulated until 1968 before being replaced, in its turn, by a H3N2 pandemic strain (Taubenberger and Morens 2010). In 1977, the H1N1 strain surfaced again (Webster and Kawaoka 1994).

The genes coding for these glycoproteins can reassort (i.e. reshuffle) thanks to two processes known as *antigenic drift* and *antigenic shift*. The former consists in the accumulation of point mutations in the genome of the virus, modifying both the shape and the electric charge of viral surface antigens and preventing their recognition by the antibodies of the host that were developed in reaction to previous exposures to the virus. The need to update the influenza vaccines every year illustrates the “evolutionary success” of antigenic drift. The latter refers to the introduction of whole or part of avian influenza genes into viruses that circulate among human populations. In particular, the introduction of the hemagglutinin gene (HA) is often hailed as the responsible factor for increased virulence (Bush 2007). The fast reassortment of nucleotides and the high rate of mutation in influenza viruses results in influenza posing a continual threat for human and animal health. Because of this, influenza is regarded as being a continually “re-emerging” disease (Webster and Kawaoka 1994).

The natural history and ecology of influenza A virus has been extensively studied (Webster et al. 1992; Webster 1987). Its natural reservoir is believed to be wild water-fowl, which is indicated by the fact that species of wild duck are not affected by the virus and remains “healthy”. The virus replicates inside the host, mostly in the intestinal tract, and is then washed into the ponds where ducks live (Webster 1993). The relative harmlessness of this (evolutionary) relationship is similar to the way myxoma virus is adapted to its natural host, as studied in chapter 4. Genetic reassortment (antigenic drift) occurs especially in swine which act as “mixing vessels” for the viral strains and are considered the intermediate host between birds and humans (Webster and Kawaoka 1994).

A WESTERN ORIGIN

A first important aspect of the 1918 influenza pandemic is its possible Western origin. In part because of the extensive pig-duck farming China was singled out as the possible origin of most influenza pandemics. Whereas most pandemics to have befallen man have come from China (Morse 1993, 17) the "Spanish" flu originated (likely) in ... France as early as 1916 causing acute respiratory symptoms closely resembling the phenotype of the disease during the 1918-19 pandemic (Oxford et al. 2005; 2002). Morse and his colleagues recently argued that there was an early wave of influenza in New York between February and April 1918 (Olson et al. 2005). The precise geographical origins of the 1918 pandemic are still a matter of debate, however. [148]

The world's deadliest flu pandemic kicked off in October 1918 and after a few months only, the virus killed between 30 and 40 millions of people (Philips and Killingray 2003; Crosby 1989; some estimate deaths to be about fifty millions, see McNeil 1976). Three successive waves of influenza swept all five continents in 1918, the second one being the most lethal of them. The first wave (or the "spring wave") of the flu started in March in the U.S. (Mid West) before moving to Europe, then to Asia and North Africa before reaching Australia in July 1918. The second wave (or "fall wave") was highly devastating and rapidly went extinct after causing millions of deaths worldwide. It started in late August 1918 and within one week there were reports of the virus coming from distant cities including Boston (US), Freetown (Africa) and Brest (France). This second wave lasted until November. The speed at which the virus circulated makes it difficult to pinpoint one specific location as being "the" source of the pandemic but, as pointed out, a Western origin appears to be the most plausible hypothesis. Early reports indicated a further third wave that hit in the first months of 1919 (Burnet and Clarke 1942; Barry 2004a).

AGE GROUP MORTALITY

During an attack of influenza most people die of secondary infections as often death resulted from bacteria invading lungs of immunocompromised individuals (Burnet and

[148] On the history the 1918 influenza pandemic see Barry (2004a) and the now classic book on influenza by Burnet and Clark (1942). Langford (2005), however, argues that the flu pandemic originated in China.

Clark 1942). During the 1918 pandemic the symptoms lasted generally between 2 and 4 days and could, more rarely, be extended up to two weeks. The respiratory disease was characterized by fever, body pains and often severe headaches. Without the possibility of treating patients with antibiotics, bacteria turned "those vital organs [lungs] into sacks of fluids [...] effectively drowning the patient" (Philips and Killingray 2003, 5). People therefore died within a few days only of hemorrhagic pulmonary oedema and other lung afflictions (Bush 2007; see also Taubenberger et al. 2000). A second striking aspect of the 1918 influenza pandemic is the young age of the victims, which was qualitatively distinctive: most of them were men, supposedly healthy, of between 20-40 years old (some say 25-35), irrespective of whether the country was involved in the war or not. Instead of forming a U shaped mortality curve, the shape of the 1918 pandemic was W shaped. An additional peak (the central peak in the W) represents the male victims of the flu. The figure 6 (below) shows the U shaped curve of 1917 and the W shaped one of 1918. The distribution of deaths on this curve reflects the virulence of the pandemic and underlines the pattern of mortality of a group usually not affected by seasonal flu.

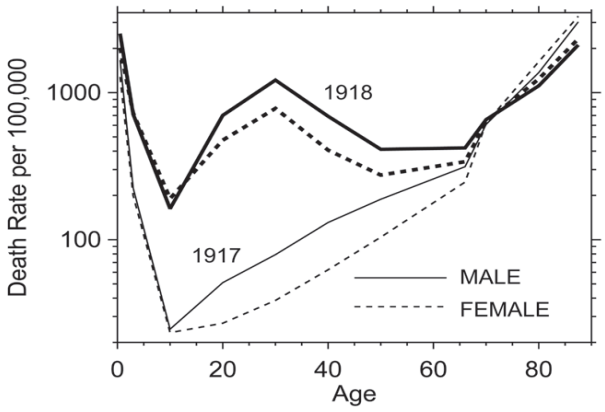

Fig. 6. Age distribution of death rates from influenza and pneumonia in the United States death registration area, 1917 and 1918. Death rate is deaths per 100,000 person-years lived. Data from US Department of Health, Education, and Welfare 1956. In Noymer (2010, 141)

EXCEPTIONAL VIRULENCE OF THE PANDEMIC

A third significant feature of the 1918 pandemic, already mentioned, is its lethality: the disease was of exceptional virulence and the pandemic made more victims than the First World War. This central aspect was recognized by virtually everyone as being somewhat unusual and very specific to this pandemic. Indeed, influenza type A viruses is not at all uncommon, as it already circulated in human populations since a few centuries when the 1918 pandemic broke out. In the United States only, annual death toll related to seasonal influenza are estimated to be about 30 000 individuals (Thompson et al. 2003). Seasonal outbreaks of influenza normally last a few weeks and then disappear abruptly; they result from influenza viruses present in human populations able to infect individuals thanks to antigenic drift. On occasions, however, the virus can infect up to 40% of the world population. During these pandemic years, in contrast, the number of deaths rises way above the average, causing millions of victims all around the globe. During seasonal epidemics strains of influenza type A and B can sometimes coexist, if at different frequencies among populations.

In the mid twentieth century, leading British bacteriologist Wilson Smith, co-discoverer of the viral nature of influenza in humans, cast doubts on the possibility that the exceptional virulence could be linked to a particular genetic or molecular structure of the virus alone; that is, he rejected a pathogen-centered (or wholly endogenous) explanation. According to Smith

> if we had the chance of getting a 1918-19 strain of virus now, it is at least conceivable that, on comparing with the Asian strain, we might find no difference in *intrinsic virulence* at all, but the *conditions in the human population* during the two epidemic periods might have affected the degree of heterogeneity displayed by viruses possessed of the same intrinsic virulence" (1960, 77; emphasis added).

Smith was then commenting on a paper given by Edwin Kilbourne, also a British virologist specialist of influenza, who had just argued that the greater virulence of the 1918 pandemic was due to a combination of "the emergence of a new antigenic type in a population with little specific immunity" and "the dislocation of and crowding of wartime

which favoured not only dissemination and high dosage of virus but spread of bacterial pathogens to an unusual degree" (Kilbourne 1960, 74). In his paper Kilbourne emphasized the role of host susceptibility in its environment when measuring the virulence of a pandemic and argued that "study of the host and his environment are more crucial to the interpretation of virulence than laboratory study of the virus itself" (1960, 71).

Taking a broad exogenous point of view, Kilbourne had argued that the exceptional virulence could not be attributed to the viral structure alone, a widely spread position then. Indeed, Macfarlane Burnet, who attended this meeting too, had promoted the "ecological point of view" of infectious diseases since the mid-1940s, contributing in the formation of a distinctive thought-style. Reductionist attempts to locate virulence within specific genes or other mobile elements (i.e. plasmids) were met with scepticism by people like Burnet who were particularly interested in large-scale ecological processes and in the formation of evolutionary and physiological equilibriums between hosts and parasites. For Burnet "there are no virulence genes as such". For him, virulence is "an epiphenomenon of the processes by which the virus survives in Nature in relation to the full totality of the environment". The concept of virulence, finally, can only be clarified by "using this ecological approach" (Burnet 1960, 1-2).

It is noteworthy that these reactions occurred in the 1960s. Ecologically-minded biologists like Burnet, Smith and Kilbourne were also reacting against the growing place of molecular biology since the 1960s and its characteristic vision of life process and the life sciences, as described in chapter 5. This is how we can interpret Edwin Kilbourne's remark that "ironically in this era of molecular biology, the control of no infectious disease has yet depended on understanding its molecular mechanisms" (1977, 1228). Similarly, when Burnet gave a "tilt" at molecular biology in 1966, he criticized the "dogma" that "there is nothing substantial in biological research apart from working out the implications of the sequence of nucleotides in DNA" (1966, 37). For him, genes are not the whole story and researchers also must consider the ecological context in which host and pathogen's relations develop.

EVOLUTIONARY EPIDEMIOLOGY AND ENVIRONMENTAL EXPLANATIONS

The trade-off model of virulence (chapter 4) was applied by "evolutionary epidemiologist" Paul Ewald to the case of the Spanish influenza pandemic. With this label Ewald attempted to bring together various disciplines including public health, ecology and epidemiology under a broader, more integrative and evolutionary perspective. I first describe the trade-off model in general terms before moving on to Ewald's application of it to the case of the 1918 influenza pandemic.

The development of the trade-off model provided new ways of measuring, predicting and, therefore, explaining the evolution of virulence in biological systems. The model rests on the idea that virulence cannot increase beyond a certain point without at the same time inflicting damage to the host which would, in turn, be harmful to the pathogen; there is a trade-off, or a compromise, between virulence and transmissibility. The highest possible level of virulence, however, is not always the best (optimal) strategy to increase parasite's transmission, as the host is likely to die in the process. This was very much the reasoning behind the conventional wisdom. Yet, in cases where inflicting damage actually increases the chances of the parasite to be transmitted to a new host, high level of virulence is likely to be selected for (Combes 2010, 128). This model is neutral with respect to causes and only relates to observable effects, however.

This model focuses primarily on pathogen's population and their evolution, not on the host because generation time for hosts (here, humans) is much longer and so evolution in the host population is likely to be slow. Another dimension of the model is that it does not concern itself with morbidity (at least not explicitly). Thus, symptoms like pain or injuries are not taken into account by the trade-off model and are implicitly integrated (some would say collapsed) with other variables like host recovery and parasite transmission (Levins 1996). This assumption impacts on the ways in which virulence will be measured and operationalized. As indicated in chapter 3 virulence tends to be measured and defined differently by each discipline. Whereas for doctors morbidity (illness) is a key feature of virulence, for evolutionary biologists or population biologists host's pathological factors do not need to be taken into account when measuring

virulence as what matters is host's reduction in fitness. The trade-off model is often given in a mathematical formula as follows (chapter 4):

$$R_0 = \frac{ßN}{\alpha + b + v}$$

> Where R_0 is the number of infections after a first infection. It serves as a measure of Darwinian fitness. What is below the lines are α (virulence), b, the rate of microparasite independent-mortality and v is the rate of recovery of the host. Those variables are linked. This equation states that the measure of Darwinian fitness (R_0) is directly proportional to its transmissibility, ß, at any host-density population (N) (Levin 1996, 95).

Infection where R_0 is less than 1 will rapidly go extinct. In the case of the 1918 pandemic, calculations suggest that R_0 was equal to 2 (Morse 2007, 7314). This model of the evolution of virulence does not focus one-sidedly on either the properties of the host or the pathogen, but rather on the dynamic relations of these entities at a higher level of biological organization: the ecological level. From a trade-off perspective, the evolution towards avirulence postulated by Smith and Burnet for example, turns out to be only a special case of disease evolution (chapter 3) This newly-opened niche in the study of infectious diseases based on epidemiological, mathematical, experimental, and evolutionary models led, ten years ago, to the development of "virulence management" strategies (Dieckmann et al. 2002), and to the idea of "taming" pathogens by rendering them avirulent, for example by interfering with their normal route of transmission (Ewald 1994; 1990; 1983). The latter was especially advocated by Ewald who founded a discipline he baptised evolutionary epidemiology (1988). Paul Ewald has a long-time interest in the biology of host-pathogen interactions and their implications for human health and disease. He was one of the most prominent critiques of the avirulence hypothesis, and he tried to motivate an ecological and evolutionary view of pathogen's changes in virulence, drawing attention to the fact that so far, progress towards understanding the conditions

that favoured its exceptional virulence "has largely been limited to improved understanding of the genetic mechanisms of antigenic changes and the influences of these changes and host immunity on the occurrence of epidemics" (1990, 15). Ewald criticized the magnitude of the importance given to the endogenous thought-style.

His early work on pathogen's virulence and transmission applied the cost-benefits model of the trade-off to waterborne diarrheal diseases (Ewald 1980). His study was based on the concept of "cultural vectors" and on the assumption that parasites that do not rely on host mobility for transmission should evolve towards higher levels of virulence. A cultural vector is defined as "a set of characteristics that allow transmission from immobilized hosts to susceptible when at least one of the characteristics is some aspects of human cultures" (1994; 68; see also Ewald 1988). In the case of waterborne transmission, cultural vectors include contaminated bed sheets in hospitals, sewage system carrying the pathogens, medical staff moving the contaminated water to water supplies, and so on. According to the cultural vector hypothesis, waterborne diseases can allow to become more virulent because they do not rely on host mobility for transmission (see 1994, 69), that is, the host can be isolated and still be highly contagious. In other words, a "healthy" host is not needed for transmission (in contrast with what was postulated by the avirulence model). For Ewald, acting on the cultural vectors could thus indirectly select for reduced virulence – for instance how the installation of mosquito nets can alter malarial diseases' transmission (Ewald 1999).

THE 1918 INFLUENZA PANDEMIC IN THE LIGHT OF THE TRADE-OFF MODEL

Applying the cultural vector hypothesis to the case of the 1918 pandemic, Ewald argued that host proximity was a key element in the exceptional virulence. In his book on *The Evolution of Infectious Disease* (1994) he criticized three hypotheses attempting to explain the virulence of the 1918 flu pandemic. These explanations 1) postulates a recent entrance of the flu virus into humans; 2) identifies another pathogen as the cause of the 1918 pandemic; 3) or specifies that virulence results from rapid serial passages in hosts. Pointing out limitations to each of these hypotheses, Ewald tried to grasp the problem of the evolution of virulence at a more global level. The first hypothesis is given only a short shrift by Ewald. This "proximate" explanation attributed to Steven (1981) postulates that

deaths occurred not because of the flu virus but because of another strain that struck at the same time, namely *Hemophilius influenza*. In most cases discussed by Steven, however, this bacterium is absent.

The second explanation assumes a recent encounter between the flu virus and human populations (Gorman et al. 1991). It is based on a phylogenetic analysis of nucleoprotein gene sequences called neuraminidase (NA) in swine, birds and humans, and their evolution. The analysis of this paper supports the hypothesis of a common ancestor to swine and humans at the beginning of the twentieth century, and this ancestor is alleged to have entered the human species just before 1918, thus causing the pandemic. However, according to Ewald "there is no evolutionary basis for supposing that transmission from swine to humans should be associated with particularly high virulence in humans" (1994, 114). On the contrary, he continues, a recent entrance should favour lower level of virulence because the immune system should be able to block new pathogens attempting to enter our bodies. Ewald defends the hypothesis that the immune system should be able to fight back nearly all pathogens without "a history of adaptation to humans" (1994, 39). Accordingly, recent entry of avian flu virus's genetic material into humans should, theoretically, have been controlled immunologically. Ewald's argument turns the avirulence hypothesis on its head, as he predicts that recent associations will tend to be less virulent than old ones.

The third explanation he considers stipulates that the exceptionally high virulence resulted from rapid passages in soldiers, recruits and wounded people in hospitals during the war, an hypothesis supported by both U.S. Office of the Surgeon General and microbiologists in the 1930s-1940s (see Burnet and Clark 1942). Yet according to Ewald, this explanation also leaves out an essential "evolutionary mechanism": it is based on the analogy with rapid passages of a viral strain through a series of animals (i.e. guinea pigs) in laboratory that increase virulence. Again, his argument is based on the cultural vector hypothesis. Like biological vectors, cultural vectors enhance virulence by facilitating transmission. The key point about the serial passages is that it removes the "requirement that hosts be mobile to transmit their infections" (1994, 115). Once this obstacle is lifted nothing (a priori) stands in the way of a steep increase in virulence. In laboratory context this is achieved artificially by the experimenter who inoculates different animals with

artificially selected viral or bacterial strains; in the field, however, this selection process resulted from another cultural vector, namely the warfare conditions.

From a trade-off model perspective, pathogens' rate of replication within a host (R_0) is balanced with the probability of its being transmitted to new host (May and Anderson 1983). If transmission is not easily achievable, levels of virulence are expected to be rather low. But if transmission is facilitated, for one reason or another, then high replication (and so high virulence) is expected to occur. In the trenches during the Great War, conditions were such that transmission was maximized and with it, the observed level of virulence. As postulated by the trade-off model, the density of the population (N) influences the level of virulence. In this case, the high density resulted from the proximity of the soldiers in the trenches. This, in turn, resulted in the unusual situation that immobilized individuals who normally should not be able to infect new people (because they would be isolated in a hospital), were now easily able to transmit the infections.

Similarly, removing wounded soldiers from the trenches and transporting them to war hospitals facilitated transmission. The constant arrival of new susceptible individuals into the population resulted in maintaining a high density of infected people; and as a consequence, an equally high level of virulence.[149] Thus, for him, looking at broader context can better account for this sudden explosion of virulence than other (endogenous) kinds of explanation focussing primarily on genes or proteins' structural specificity in the viral strain. By focussing on the specific conditions prevailing during the war, Ewald shifts the burden off the molecular determinants of virulence to larger scale processes.

Ewald paints a dramatic picture of the evolution of virulence: unless measures are taken to monitor what drives evolutionary changes of virulence, he says, "we will pay the price in sickness and death not just until our activities change the environment back to a state that favors the benign forms, but rather until the evolutionary change toward benignness is complete" (1994, 115). The positive side of Ewald's argument, however, is that granted that similar conditions do not prevail again we should not expect to see

[149] The constant arrival of susceptible individuals is what keeps the epidemic going on, as the epidemiologist William Hamer demonstrated in the early decades of the twentieth century using experiments with mice (on this see Mendelsohn 1998).

another such pandemic (Ibid.). Interestingly, the other two influenza pandemics of the twentieth century were not as deadly as the 1918-19 was.

Ewald's views on the evolution of virulence did not establish a consensus within the scientific community of evolutionary ecologists. One of the problems some detected is the overtly narrow view of virulence Ewald defended. Indeed, two reviewers of Ewald's book complained that it was written in a very adaptationist tone – i.e. virulence is depicted as being always adaptive for the parasite. As a consequence, "alternatives such as virulence being non-adaptive, or virulence being a consequence of short-sighted, within-host evolution of the parasite are ignored" (Bull and Levin 1994, 1470). What these authors complained about is that virulence is a much more complex trait whose evolution can follow different routes, achieving different outcomes. According to evolutionary ecologist Dieter Ebert, virulence evolution falls within three broad categories: 1) virulence is coincidental, namely it results from a parasite finding itself in an environment in which he has not evolved to live in; 2) virulence is a parasite adaptation, i.e., it is parasite-driven, the host is too slow to evolve a response to selection. This categories comprises a) benefits-of-virulence, b) cost-of-virulence, and c) short-sighted evolution; finally, 3) virulence is the result of host-pathogen coevolution (Ebert 1999, 164). As the reviewers also pointed out, Ewald's book lacked mathematical models to support his logical argument. Yet, it is possible to articulate his views with the trade-off model, as he himself does elsewhere (Ewald 1990).

Another problem not mentioned by these authors, and possibly more important, is the lack of specific details in Ewald's war explanation of the steep increase in virulence. To make his argument stronger Ewald needs more precise descriptions of the environmental conditions in the trenches (for instance, how close were the troops? How many soldiers were there?) Finally, Ewald has also to face the problem of the pandemic (or global) aspect of the Spanish flu: if warfare conditions determined the severity of influenza in 1918, why did it become pandemic granted that other parts of the world did not experience the same conditions?

Although Ewald's account seems to suffer from a number of theoretical and empirical problems, it suggests an important point which is that changes in virulence can only be meaningfully understood, managed and therefore prevented, once the environmental conditions are specified. His argument is a pledge for greater attention to properties other than those of the virus, and without which we will not be able to understand changes in virulence. These factors partake to the ecological environment where the pandemic is believed to have emerged (in this case, the trenches, hospitals, and so on). This style of thinking reflects the idea that epidemiological explanations ought to be concerned with the global context in which biomedical phenomena occur and develop over time, not with the properties of the pathogens alone. While Ewald does not quote it, the work of John Oxford on what I would call the "War Hypothesis" supports and reinforces Ewald's conclusion by feeding in some of the missing details.

THE WAR HYPOTHESIS

While many would agree that the war is a variable that must be included, in one way or another, in the larger explanation of the steep evolution of virulence of the 1918 pandemic, Ewald is convinced that the influenza pandemic was "caused evolutionarily by the war rather than being just coincidental with the war" (1994, 115). Some ten years ago, the "War Hypothesis", as we may call it, received new support from London microbiologist John Oxford (2001; Reid et al. 2002; Oxford et al. 2005). Oxford does not claim that the Great War caused the disease, evolutionarily or otherwise, but instead that the war created the right environment for the virus to become extremely deadly. When the 1918 pandemic broke out air travel was minimal and this suggests, according to Oxford, that "earlier 'seeding' has occurred" (2001, 1857). So far as I can see, Ewald and Oxford do not cite each other's work. And yet, their respective contributions support each other by providing what is missing in each of them.

Taking an environmentally-oriented approach to understanding the evolution of virulence, Oxford and his colleagues argued that the 1918 pandemic originated in France in 1916 before going global two years later. [150] Studying the sporadic outbreaks of

[150] This research was later criticized in turn by Barry (2004b) who argued that the Spanish influenza pandemic originated in Kansas and was taken to Europe by US soldiers in 1918.

respiratory infections at British base camp in the town of Etaples in Northern France in 1916, Oxford argued that the disease's clinical picture map very precisely onto the description of the 1918 influenza: not only were the 1916 respiratory disease extremely deadly, but post-mortem examination revealed in most cases clear evidence of bronchopneumonia, while histological analyses of lung tissues indicated "acute purulent bronchitis" (Oxford 2001, 1857).

In an article published a few years later in the journal *Vaccine*, Oxford and his colleagues examined the situation one step further. Asking whether "a particular virulence gene of influenza" could be help to identify future pandemics, they concluded that surveillance and detection of emerging influenza pandemic will be better served by understanding the context that give rise to pandemics, rather than by an analysis of genetic factors. In particular, concerning the 1918 pandemic, they noted that so far "there is no clear genetic indication of why this virus [the 1918 strain] was so virulent" and that they needed closer examination of the environmental and social conditions of the time such as "population movements" to explain the exceptional virulence. They asked specifically whether "the special circumstances engendered in the war itself have allowed or caused the emergence, evolution and spread of a pandemic virus" (Oxford et al. 2005, 941). For them, the "unprecedented circumstances" of the war in Europe were critical. Back in 1918, the front was

> a landscape that was contaminated with respiratory irritants such as chlorine and phosgene, and characterized by stress and overcrowding, the partial starvation of its civilians, and the opportunity for rapid "passages" of influenza in young soldiers would have provided the opportunity for small mutational charges throughout the viral genome [...] could have been important factors in the evolution of the virus into a particularly virulent form (Oxford et al. 2002, 113).

In this quote, the authors bring together the mutations of virus, its rapid passage in soldiers, its evolution, and the role of the environment in enhancing virulence. The military camp of Etaples was subject to high traffic in 1916-1917. In addition to soldiers

moving up to the front and back, 23 0000 sick and injured individuals were in the hospitals "at any given time", making the place overcrowded and allowing the virus plenty of opportunities for "rapid passages". Overall, it is estimated that the region of Etaples hosted two millions soldiers who camped there during the war, in addition the six millions of others who occupied and fought in the trenches system that connected the English Channel with Switzerland (Oxford et al. 2005, 942). In addition, as the camp had an "extensive piggery", villagers could buy geese, ducks, and chickens, providing ideal conditions for the influenza virus to undergo antigenic shift. The extensive use of gases during the war (estimated to one hundred ton), some of which mutagenic, rendered the soldiers immunocompromised and more susceptible to influenza infections. Finally, demobilisation after the war sent soldiers back home by boat or by train, contributing to the spread of the disease by person-to-person contact (Oxford et al. 2005).

Taken together, these factors (overcrowding, immunocompromised, pig-duck farming, demobilisation) provided the conditions for the virus to go pandemic and achieve the virulence it did. Ewald had noted that if those circumstances were not recreated it is unlikely that such a severe pandemic will dawn again. What Oxford and his colleagues emphasized is that appropriate response to future pandemic cannot rest of finding genes for virulence alone; one has also to consider the context that will allow the virus to spread in a pandemic fashion.

EMERGING TECHNOLOGIES

Ewald's argument was developed in the mid-1990s when genomics was not yet the current paradigm for understanding health, disease and other biological processes. But what if the whole genome of this virus suddenly became available to scientists? Arguably, with large genetic and molecular data-sets at hand scientists would be in a better position to pinpoint the specific, molecular cause(s) of virulence in influenza pandemics so as to provide a full explanation of the pandemic. Nowadays, a renewed and stronger emphasis is put again on the molecular constituents of virulence, providing new impetus for pursuing the centrality of the endogenous further. Such factors, it is often argued, play a more important role in the emergence of disease pandemic and in causing death and morbidity worldwide, than environmental processes. Newly developed technology and

the availability of pathogenic viral and bacterial material facilitated the development of this approach towards explaining infectiousness. Once barely more than a thought experiment, this hypothetical scenario has, during the past fifteen years, grown into an international research programme, concluded with the publication of the complete influenza virus' genome map in 2005, both in *Nature* and *Science*.

As pointed out above, the viral nature of influenza was finally accepted in 1933; but all samples of the 1918 strain were thought to be long extinct and lost. Yet recently, bits of RNA of the virus were found and processed in order to generate a complete sequence of its genetic structure. After the discovery of frozen individuals killed by the 1918 pandemic and preserved in permafrost, scientists have been working on the mechanisms enabling the influenza virus to achieve unprecedented levels of virulence. This work was led by the microbiologists Jeffrey Taubenberger of the National Institutes of Health and Terrence Tumpey from the Center for Disease Control, both based in the USA. (These teams also received unexpected help from a retired Swedish pathologist). I now turn to this recent technological success, and its eventual failure to pinpoint any particular molecular feature of the flu virus of 1918 that could account for its exceptional virulence.

TRACES OF THE SPANISH FLU: FROM (SERO)ARCHEOLOGY TO PCR AMPLIFICATION

In the early 1950s scientific expeditions were organized to discover the remains of victims of the Spanish flu in the hope to find traces of the virus. One of these expeditors was a trained pathologist from Sweden who immigrated to Iowa in 1949 named John Hultin (1925-). In 1951 he was preparing his expedition to the North Pole. As part of a project funded by the University of Iowa Hultin travelled to a small Inuit village whose population was decimated by the 1918 pandemic, killing 70 people in a week which amounted to 85 percent of the inhabitants. Hoping to find preserved corpses buried in the permafrost hosting traces of the virulent infection, Hultin travelled to the Seward Peninsular of Alaska in a village known as Teller Mission (Taubenberger 2003). Digging into the cemetery of the village he exhumed lung tissues from several bodies. All attempts to culture any remaining traces of the virus of influenza from these samples, however, failed to give any result.

Hultin moved on and became a successful pathologist. Forty years later, however, in the midst of the rise of the Human Genome Project, the idea of resurrecting the virus surfaced again. In 1997 a U.S. lab-group based at the Armed Forces Institute of Pathology in Washington (D.C.) led by the molecular pathologist Jeffrey Taubenberger published a paper in *Science* titled "Initial genetic characterization of the 1918 'Spanish' influenza virus". This paper provided a first and partial genetic map of the virus from "archival formalin-fixed, paraffin-embedded autopsy tissues of 1918 flu victims" (Taubenberger 2003, 42). The examined samples were kept at, and provided by, the National Tissue Repository of the Armed Forces Institute of Pathology. As several mutations in hemagglutinin, especially on cleavage-sites, often contribute to the virulence (e.g. Hong Kong pandemic in 1968), it was hoped that the genetic make-up of the virus would disclose the secret of the exceptional virulence of 1918 Spanish influenza pandemic. The goal of the project was to characterize how the virus spread from birds to human, but also to understand the mechanism(s) of virulence. As stated by Taubenberger, their aim was to "first, to discover where the 1918 influenza came from, and how it got into people, and second, whether there were any genetic features of the sequence that would give insight into the exceptional virulence of the strain" (2003, 44).

GENETIC CHARACTERIZATION OF THE 1918 "SPANISH" INFLUENZA VIRUS

This first publication describes the technique used to obtain, amplify (PCR), and sequence the genetic material. The main finding of this paper is the confirmation, through molecular phylogenetic analyses of gene segments, that the 1918 pandemic was caused by a strain of H1N1 influenza virus, supporting the hypothesis of an avian origin of the virus spreading first to humans and then swine in the fall of 1918 (1997, 1795). In their first article, Taubenberger randomly selected 28 cases or paraffin-embedded tissues collected from army servicemen who died during the 1918 pandemic for pathological review, searching for symptoms indicative of death by influenza. Most of the individuals examined died of secondary pulmonary infection, however, a common feature of victims of the 1918 pandemic. As we have seen, Shope demonstrated how bacterial infection works together with the influenza virus in delineating the clinical picture of the disease. One case, though (1918 case1), could be linked to viral pneumonia. This one case

exhibited symptoms of acute pneumonia in the left lung combined with an acute form of brochiolitis in the right lung. This lung pathological characteristic was typical of a "primary viral pneumonia".

Focussing on case1 researchers performed control amplification of reverse-transcribed genetics of the nine gene fragments of the 1918 virus using the technique of polymerase chain reaction (PCR). They then carried out phylogenetic analyses based on the gene sequences to reconstruct the genealogical relationships between these elements. It was concluded that the genetic sequence of this strain was different from every other influenza strain, and that it was more closely related to strain in birds than in mammals. This partial analysis of the genetic map of human influenza was soon followed by a complete sequencing operation of the hemagglutinin gene (HA) – a gene long believed to be "pivotal" in the pathogenicity of influenza A viruses (Webster 1987; see also Cox and Bender 1995). This gene codes for a protein situated on the surface of the virus that plays a crucial role in allowing the virus to bind to host's cells. If the virus is able to spread to another species this means it has somehow (through antigenic drift) acquired a new protein that enables it to bind on a different receptor.

ORIGIN AND EVOLUTION OF THE 1918 INFLUENZA VIRUS HEMAGGLUTININ GENE

In 1999, the team published another article on the "Origin and evolution of the 1918 "Spanish" influenza virus hemagglutinin gene". Among the authors of the study– including Ann Reid and Jeffrey Taubenberger – is Johan Hultin, the pathologist who attempted to find traces of the influenza virus in Alaska in the early 1950s. After having read the 1997 *Science* paper, Hultin wrote a letter to Taubenberger offering to go back to Brevig Mission in Alaska to look for fresh samples of people who died of the flu (Taubenberger 2003, 43). At the same time, another mission in the North Pole was underway. It was led by Kirsty Duncan, a geographer at University of Winsdor in Canada. Their goal was to uncover bodies buried in a mine in an island off Norway in the Polar Circle. The mission however planned in advance and well-funded, was largely unsuccessful. The ground in which the miners were buried was unlikely to yield any significant result given that it had thawed

and later refrozen, leaving scientists no hope to recover the virus "alive", or in a condition suitable for future culture. [151]

Against all odds, Hultin was successful this time. After he received the approval of Taubenberger he set out to Alaska for a second time and there he found *in situ* frozen lung biopsies in August 1997. Once in the village, he was granted permission from the council to dig the graveyard again and with the help of a few villagers he unearthed the body of a thirty years old woman after four days of work. He called her "Lucy". Opening up her chest he found two frozen lungs which he rapidly sent to Taubenberger's laboratory in Washington, along with some tissues taken from three other frozen corpses.

In the (1999) paper Reid et al. reported about the full sequence of the hemagglutinin gene using RNA fragments from case1 discussed in the first article. They investigated three cases histories to find evidence of influenza RNA. The first one was a 21 year-old man who died at Fort Jackson in South Carolina. The pathological records indicate he had pneumonia and influenza symptoms. He was admitted to the camp hospitals on September twentieth 1918 and died within 6 days. The autopsy records also indicate that his left lung showed he suffered from an acute and fatal attack of pneumonia, whereas his right one showed acute bronchiolitis and alveolitis – a clear sign, as mentioned above, of influenza infection. No RNA was found in the left lung. However, the team performed a minute microscopic analysis on the paraffin-embedded tissue of the right lung and discovered that the tissues tested positive for influenza RNA. The fragments of five genes (about 150 nucleotides long) were sequenced, amplified thtrough PCR and determined.

The second case was also a male soldier. He was 30 years old and was based at Camp Upton in the State of New York. He was admitted with pneumonia and died within 3 days on the 23 of September 1918. Microscopic examination of his lungs by Taubenberger revealed acute pulmonary oedema and acute bronchopneumonia. Again, formalin-fiexed, paraffin-embedded samples of lung tissues tested positive for influenza RNA, the sequence of which were also no longer than 150 nucleotides.

[151] This piece of information is taken from an article "The virus detective" published by the San Francisco Gate, Sunday, February 17th, 2002.

The third case history was the one found by Hultin in Brevig Mission, Alaska. With the help of the villagers Hultin had exhumed the bodies of four victims of the influenza pandemic of 1918. To preserve the tissues, the biopsies collected *in situ* were placed in "formalin, alcohol fixatives, and RNAzol" (Reid et al. 1999, 1652). All tissues displayed clear signs of acute form of pulmonary haemorrhage and oedema. Only one of the cases, the female subject, "Lucy", was positive to influenza RNA, however. Using the sequences of these three case-histories the Washington-based team worked out the genealogical relationships between them. Their analysis concludes that the avian virus that caused the pandemic entered human populations between 1900 and 1915, following the modification of the binding site on the HA protein. In 2005 Taubenberger and Tumpey published two separate articles in *Nature* and *Science*. The first one provided the complete genomic sequence of the 1918 influenza virus and the second one revealed the methods used to artificially reconstruct it. Yet, even before the complete genetic map became available, it became unclear whether the genes of the virus had disclosed the reasons of its exceptional virulence.

THE MISSING MUTATION: THE LIMITS OF GENOMIC ANALYSES

The Washington team reported that a cleavage-site mutation that plays a crucial role in the virulence of the Hong Kong pandemic in 1968 *was not found* in the strain obtained from the South Carolina case. Sequencing the cleavage site in the RNA of the virus obtained from the Brevig mission case and New York case also confirms that this mutation was absent. Inquiring into this mutation site (hemagglutinin) understood as a key determinant of virulence was a central motivation of Taubenberger. In effect, "it would have, as Taubenberger wrote, "offered an appealing explanation of the 1918's flu virulence". However, he concludes, "the 1918 strain (as confirmed by all three cases) does not possess a mutation at this site" (2003, 45; Reid et al. 1999). The (1999) paper ends elusively with some remarks about the complex, likely polygenic nature of what determines the virulence of a particular strain – and with the hope that more sequencing would "shed additional light on the nature of the 1918 influenza virus" (1999, 1656). In other words, the secrets of the Spanish influenza "remain elusive" as the virologist Robert Webster (1999) wrote in his commentary of the article. Webster commented that such

"biological properties" [i.e. virulence] may "not be resolved". Furthermore, he suggested that the hype of the genome sequencing enterprise can only provides a partial explanation of this phenomenon. For Webster, "the entire gene sequence is unlikely to reveal the secret of the high pathogenicity of the 1918 Spanish virus" (1999, 1165).

Another molecular explanation of the Spanish flu pandemic emerged in 1998 from another research team. Goto and Kawaoka, in the *Proceedings of the National Academy of Science*, published a paper on a "novel mechanism for the acquisition of virulence by a human influenza A virus". They argue that a change in another protein – neuraminidase – able to increase the cleavage of HA can bring about higher levels of virulence. In fact, they even suggest that a change in a single amino-acid sequestering plasminogen may facilitate HA cleavage. The authors are careful, however, stating that they "do not conclude that single mutation will convert nonplasminogen-binding NAs to efficient plasminogen binders, thus rendering the virus highly virulent" (1998, 10228). Yet, they confess that it is "tempting to speculate that the 1918 pandemic strain [...] may have acquired its unprecedented virulence from the mechanism we describe" (Ibid).

But as Taubenberger pointed out, such a change in amino-acid was not present (or at least not observed) in the 1918 neuraminidase sequence – a similar conclusion his own team reached the same year (2003, 45; 1988). Taubenberger and Tumpey, however, acknowledged the lack of evidence provided by the molecular structure of the virus:

> Sequence analysis of the 1918 influenza virus from fixed and frozen lung tissue has provided molecular characterization and phylogenetic analysis of this strain. The complete coding sequence of the 1918 nonstructural (NS), hemagglutinin (HA), neuraminidase (NA), and matrix (M) genes have been determined; however, *the sequences of these genes did not reveal features that could account for its high virulence*" (Tumpey et al. 2004; emphasis added).

Yet *there is* something special about the HA protein that contributes to enhanced virulence: using a mouse model, another team of molecular pathologists (Kobasa et al. 2004) showed that when the HA protein taken from a 1918 viral strain was inserted into mice it confers high pathogenicity and facilitates lung infections. Infected mice show 39, 000 times more virus particles after infection with the 1918 strain than with other viral

strains like Texas virus. Moreover, all infected mice died after 6 days following infection with 1918 strain, while all survived when infected with the Texas virus (von Bubnoff 2005, 794). The particular structure of the protein responsible for such pathological effect remains to be found, however.

To sum up, the two most important glycoproteins allowing viruses to invade host's tissues – hemagglutinin (HA) and neuraminidase (NA) – are significant molecular determinants of the virulence of influenza pandemics in 1957 and 1968. Considerable explanatory power was placed on these special proteins that seemed to provide a firsthand, adequate, simple and elegant mechanism to account for the exceptional virulence of the 1918 pandemic. Indeed, the "most popular theory" was that the 1918 virus had "unique pathogenic properties, most likely encoded within the hemagglutinin protein" (Holmes 2004). In addition, it was firmly believed that identifying molecular and genetic basis of virulence could not only provide a window into the most devastating epidemic of modern times, but also help to prevent and predict those to come. Overall, the remarkable technological success – i.e. the retrieving and sequencing of the 1918 avian virus – promised nothing less than unlocking one of the oldest, well-kept secrets in the whole medical history. After sequencing the genome of the 1918 viral strain that killed perhaps up to forty million people, both factors were found to be lacking in the killer strain, however.

THE TWO SIDES OF DARWINIAN EXPLANATIONS: COMMON DESCENT AND NATURAL SELECTION

It would be misleading to conclude that his work is not informed by evolutionary thinking. In effect, Taubenberger's team provided the first molecular characterisation of the genealogical tree of the Spanish flu virus – a Darwinian piece of work in some of its most orthodox aspects. But what kind of Darwinian thinking is this? Building on Michel Morange's analyses I would like to suggest that there are two (compatible but separated) features of Darwinism at work in the research of Taubenberger and Ewald – and more generally in the fields of molecular pathology and evolutionary ecology where the focus is

on the concept of virulence.[152] This divide between aspects of Darwinian thinking also reflects the larger divide between styles of reasoning.

Michael Ruse (1992) has long pointed out that the term "Darwinism" carries two broad meanings. It can be used firstly in a metaphysical sense to characterize change, development and transformation in the natural world. In this sense, the concept of Darwinism is older than Darwin himself. This first interpretation is not immediately relevant for the present discussion. Another sense of Darwinism is important to acknowledge, however. In this second sense, Darwinism is a scientific notion that comes out directly of the work of Darwin and it can refer to the *fact* of evolution, the *paths* (phylogenies) of evolution, and the *mechanism* (natural selection) of evolution (1992, 77; Ayala 1985).

According to this second interpretation, the work of Taubenberger, on the one hand, and that of Ewald and Oxford, on the other, falls on different side. While both accept evolution as a fact, the former is interested in the "path" of evolution, while the later focuses on the "mechanism" of evolution. As described above, the research of Taubenberger focuses on precise and minute description of the small steps that allows viruses to infect more than one species; this work focuses especially on tracking the changes in nucleotides and charting the genealogical relationships between the strains of influenza. Ewald, in contrast, takes a broader view and asks why those mutations were selected, what were the selective pressures that drove them to be passed on and conserved in the gene pool, and especially, what is the role of the milieu, largely understood, in shaping virulence. Living forms and their milieu being indivisible, understanding one requires understanding the other as well. These two approaches correspond to two different ways of introducing evolutionary questioning into functional biology (Morange 2010, 114).

[152] What Morange (2011) characterises as two possible definitions of Darwinism is firstly, the one centered on natural selection on small variations as the central force in the evolution of populations; the other, broader approach to Darwinism also includes epigenetic mechanisms, constraints, lateral gene transfer and symbiosis as important key evolutionary mechanisms. The contrast I have in mind is rather between describing small variations and explaining their adaptive advantage by identifying a mechanism (i.e. natural selection).

To put it differently, although the centrality of the concept of natural selection is not in dispute, the ways in which Taubenberger and Ewald (and other evolutionary ecologists) understand these processes differs significantly on one important point: whereas the former describes the small incremental steps leading to the high, observable level of virulence, the latter is "more ambitious" (Morange 2010, 114) and looks for a plausible, eventually testable evolutionary scenario leading to the accumulation and conservation of these small, gradual changes. In other words, the second approach seeks not only to describe organic changes leading to the formation of new viral strains, for example, but also attempts to give an account of the adaptive value of these transformations in the particular milieu in which the microorganisms lived, reproduced and eventually, died.

These two faces of evolution are well known in the history of biology. According to Mayr this dichotomy was still very common in the 1960s "Even today, Mayr wrote "there still are some zoologists to whom the term "evolution" signifies little more than a determination of homology, common ancestors, and phylogenetic trees". However, he agreed that "by far the majority of evolutionary biologists" [...] "have shifted their interests to a study of causes and mechanisms of evolutionary change and to an attempt to determine the role and relative importance of various factors" (1965). Generating molecular phylogenies is not doubt useful but it should not lead one to neglect environmental causes at once.

CONCLUDING REMARKS

In this chapter I explored the history of the ancient and modern concept of emerging disease which was then applied to the example of the Spanish influenza pandemic. I argued that although the concept provided a platform to rethink the threats posed by infectious diseases in the mid-1990s, bringing together two distinct styles of reasoning to bear on the problem – the molecular and the ecological – genuine articulation of different explanatory frameworks remain marginal.

In the face of the lack of evidence supporting a molecular mechanism of virulence, and in the light of the limitations of environmental-evolutionary explanations, however, one could expect researchers to seek support in each other's work in order to

complement their researches, and moving beyond the epistemic limitations of their own disciplinary boundaries. Yet it is striking to note that Reid, Taubenberger et al. (1999), on the one hand, and Goto and Kawaoka (1998), on the other, reached a conclusion diametrically opposed to that of Webster (and Oxford as well): in order to explain better (if at all) the influenza pandemic, more sequencing is needed. Instead of considering other possible explanations of the exceptional virulence (i.e. ecological explanations) they persist in their attempt to provide a complete explanation within a single explanatory framework. Obviously, though, the research programme developed by Taubenberger, Tumpey and others could not be ended too soon, especially after gathering immense publicity and funding, even though it failed to provide the specific answers the research team was looking for. Their results and methods now enable world-wide researchers to understand the molecular differences between various influenza trains and have led to some interesting results. In fact, it is expected that these scientists will keep working within their "thought-style" until all possibilities of finding the key to the exceptional virulence have been looked at and examined in every detail. From this point of view their persistence in finding a molecular magic bullet makes perfect sense, although from a public health and biosecurity point of view, their research raises important ethical questions (Aken 2006). The next chapter will examine some of these issues in the light of dual-use technologies in the life sciences such as the ones that permitted the re-creation of the influenza viruses and other deadly pathogens.

The divide between the two styles of reasoning is not yet fully resolved despite the role of the concept of emerging disease in bring both molecular and ecological perspectives on infection together. However, molecular pathologists sometimes try to integrate a more environmental perspective, with the result that evolutionary ecologists and molecular pathologists sometimes talk at cross purposes. For example, in one of the last publications of Taubenberger and his colleagues, the authors conclude that the diminution of severity of influenza pandemics over time "is surely due in part to advances in medicine and public health, but it may also reflect viral evolutionary choices that favors optimal transmissibility with minimal pathogenicity - *a virus that kills its host too fast or sends them to bed is not optimally transmissible*" (Morens, Taubenberger, Fauci, 2009, 229; emphasis added). This statement is tantamount to saying that the biological

interests of the virus will be best served by evolving lower virulence over time in order to facilitate transmission to new hosts, an explanation that rests on the avirulence model (chapter 4). This is all the most surprising given that Anthony Fauci, on the authors, has long criticized this view (see Fauci 2005). We have seen why and how the new perspective on the evolution of infectious diseases challenges this core principle. According to the trade-off model infectious diseases that can infect people even when the host is immobile are likely to become more virulent over time (Ewald 1983). On the trade-off model the optimality of transmission is balanced with the optimal level of virulence that can possibly be achieved without paying too high a cost. Yet, if conditions are such that transmission is facilitated and does not depend on a healthy host moving around, then the levels of virulence are expected to rise significantly. This is the "evolutionary mechanism" that transformed an influenza epidemic into a world pandemic, at least according to Paul Ewald (1994).

What looks as a sign of determination in science can also reflect a lack of communication between distinct scientific communities (if not an outright refusal to see how other kinds of explanation can be put into play), and more broadly reflect the problems of interdisciplinarity. This situation may be due to the fact that functional explanations such as those constructed in molecular biology tend to appear "self-sufficient", as Michel Morange recently put it (2011). This epistemological obstacle means that, for many, there is no need to complement molecular explanations with ecological considerations. The past 15 years of research in microbiology and many areas of the life sciences, indeed, seem characterized by a "deluge" of analyses of the molecular constituents of virulence, following the rise of bacterial pathogenomics (Pallen and Wren 2007), and the launching of the Influenza Genome Sequencing Project. This project is hosted by the National Institute of Allergy and Infectious Diseases where Taubenberger is now head of the pathogenesis and evolution section in the Laboratory of Infectious Diseases.

But there is another, fast-growing approach to virulence which has developed since the 1970s in the wake of the AIDS pandemic and the end of optimism regarding the decline in infectious diseases. This ecologically-oriented trend developed the trade-off model and indicated the influence played by environmental changes broadly conceived

and other factors on the level of virulence. A recent article has underlined the divide between finding biological mechanisms for virulence and the selective pressures that led to their conservation and transmission, pointing out that "each of these topics is generally discussed with little consideration for the other" (Brown et al. 2006). Thus existing, complementary explanations of the exceptional virulence of the 1918 strain, are out there but the architect of the resurrection of the Spanish flu project remain somehow blind to them. Branches of sciences can sometimes be surprisingly disconnected, separated by epistemic gaps, professional or institutional barriers. It is plain that the bulk of the research on influenza nowadays is done on the molecular side. But can virulent factors alone provide a genuinely comprehensive explanation of the 1918 pandemic and the others that occurred during the twentieth century? Can the discoveries of (a few) point mutations in the virus' genetic code also explain why they were selected and why the virus spread so fast across the globe? As experimental evolutionary biologist Richard Lenski nicely put it, "mutations alone cannot drive epidemics". Indeed, "the necessary genetic variability of the pathogen must exist and so must the appropriate selective conditions for the spread of hypervirulent mutants" (1988, 73). To go back to Grmek once more, "certainly no one can explain the origin of an epidemic of an infectious nature without beginning to take into consideration the biological properties of the infectious agent. But that is only one step along a path that leads to a full historical comprehension" (1990, 156).

One might want to ask how generalizable the analysis provided here is. The following quote is taken from a research on *Yersinia pestis*, the pathogen that causes plague or the Black Death in the fourteenth century. After sequencing and reconstructing the plague virus, the authors of the study came to a similar conclusion as Taubenberger regarding the gene-only explanation of changes in virulence over time.

> Regardless, although no extant Y. pestis strain possesses the same genetic profile as our ancient organism, our data suggest that few changes in known virulence-associated genes have accrued in the organism's 660 years of evolution as a human pathogen, further suggesting that its perceived *increased virulence* in history *may not be due to novel fixed point mutations* detectable via the analytical approach described here. At our

> current resolution, we posit that *molecular changes in pathogens are but one component of a constellation of factors contributing to changing infectious disease prevalence and severity*, where genetics of the host population, climate, vector dynamics, social conditions and *synergistic interactions with concurrent diseases* should be foremost in discussions of population susceptibility to infectious disease and host–pathogen relationships with reference to *Y. pestis* infections (Bos et al. 2011; emphasis added).

The authors of this article indicate that a molecular approach provides an incomplete picture when applied in isolation, and that a complementary ecological perspective is needed. Indeed, the study did not reveal any significant genetic or evolutionary change in 600 years that could explain the virulence of plague in the fourteenth century. Furthermore, the conclusion of the study emphasizes precisely the point of this chapter, namely that a full understanding of the evolution of virulence in infectious diseases requires a multi-dimensional approach that address host's resistance, ecological environment, and in the case of emerging diseases the interactions between the different diseases in a well-defined geographical area over a given time period.[153]

[153] The remark about the "synergistic interactions with concurrent diseases" calls for a renewed attention to the concept of pathocenosis as defined by Grmek in 1969.

CHAPTER 7: RECONSTRUCTING VIRUSES, CREATING DISEASES: SOCIAL AND ETHICAL ISSUES IN SYNTHETIC BIOLOGY, GENOMICS, AND SYNTHETIC GENOMICS

INTRODUCTION

This final and shorter chapter purports to explore some aspects of the social and ethical issues that arose during the reconstruction of the 1918 viral strain, particularly in the context of genomics and synthetic biology, but also in relation to the scope and meaning of the concept of emerging diseases more generally.

In the early 1990s, both the U.S. Institute of Medicine report on *Microbial Threats* (Lederberg, Shope, and Oaks 1992) and *Emerging Viruses* (Morse 1993) stressed how emerging infectious diseases are posing a renewed threat to public health that needs to be addressed on a global scale, from the combined perspective of ecological and molecular approaches. At the same time infectious diseases were being rebranded as "emerging" they were related to questions of biosecurity. In other words, the discourse on emerging diseases was parallel to U.S. discourse on homeland security. Indeed, the IOM report (1992, v) was itself framed as a defensive document, proposing solutions to protect the U.S. citizens from the threat of emerging diseases – a threat seen as coming mostly from the South with the potential to infect the North. In fact, the problem of emerging diseases and biosecurity was being dealt with by the exact same two men who headed the influential report and the conference on emerging viruses – Lederberg and Morse – leading, as it were, to a reconceptualization of emerging disease in warfare terms. It is not surprising as, for many years before the writing of the the IOM report, Lederberg was science policy adviser to the U.S. government and also advised the NASA on questions of exobiology. Lederberg regarded emerging diseases and bioweapons as two domains where the operations of "containment" and "detection through surveillance" are necessary. Morse, on the other hand, was program manager in the U.S. Department of Defense at the Defense Advanced Research Projects Agency. Issues of emerging infections were thus from the very beginning intertwined with questions of gloabal biosecurity (Weir and Mykhalovski 2010, 38).

The concept of emerging diseases has focalized international efforts to contain infectious diseases within well-defined geographical and temporal limitations. Emerging diseases, understood as those whose incidence had increased in the past two decades, had to be kept outside the U.S. frontiers (Lederberg, Shope, and Oaks 1992). It is thus unsurprising that when the concept of emerging disease came about in the scientific and political spheres in the mid-1990s, starting in the U.S. and Canada before migrating overseas and reaching the World Health Organization a few years later, it was immediately linked to questions of homeland and global biosecurity. The question was: in a world where "diseases know no border", how best to prevent communicable diseases from invading other countries? How can they be contained and controlled within specific geo-political borders in a world where ecological interconnectedness, thanks to global travel, reigns?

THE EMERGENCE OF A NEW FORM OF BIOLOGICAL THREAT

With the (re)creation of the Spanish influenza strain and a few others (e.g. *Yersinia pestis*, polio virus, Fouchier's H5N1), a different form of biological threat arises, however, one that requires different political, institutional, and legal response mechanisms. In a word, while the threat of emerging infections was mostly perceived as coming from *outside* Northern-hemisphere countries, it now appears to be growing from *within* the heartland of Western countries itself. Instead of stressing possible disease invasions in previously unexposed countries (or with only low incidence of a particular disease), recently developed technologies in synthetic biology and genomics science have opened-up the possibility to artificially create new disease, or to resurrect old ones such as the plague, the influenza strain responsible for the 1918 pandemic, and the polio virus (Bos et al. 2011; Taubenberger et al. 2005; Tumpey et al. 2005; Cello, Paul, and Wimmer 2002). This change in the nature of threat generated concerns regarding the desirability (and indeed, the feasibility) of disease eradication as both a desirable and worthy goal of public health medicine (Caplan 2009).

The combination of chemical analysis of genetic material and computer sciences allowed scientists to redesign the genome of some organisms like viruses, an approach often referred to as "synthetic genomics". [154] Since 2002, scientists have demonstrated that it is technologically feasible to artificially synthesize a pathogen (e.g. poliovirus) using biochemical and *in vitro* procedures, by "solely following instruction from a written sequence" (Cello, Paul and Wimmer 2002, 1). With the development of synthetic genomics, researchers do not need sophisticated recombinant genetic technology anymore to recreate viruses or other pathogens in laboratory; they are free to pursue their research goals "without being bogged down in the underlying molecular manipulations" (Garfinkel, Endy, Epsin, and Friedman 2007, 7). However, this new technology raises serious concerns regarding the very real possibility "to generate Select Agents *de novo*" (NSABB Report 2006, 2). As Ian Ramshaw – on of the scientists involved in the mousepox experience in Australia (Jackson et al. 2001) – once summarized "you can send an e-mail stipulating the sequence you want synthesized. The DNA sequence comes back. You put it in a small plasmid and if it is a human pathogen, you inject it into a human and it makes the virus" (quoted in Selgelid and Weir 2009, 23). [See figure 7 below]. Emerging diseases can thus be fabricated. However we understand the nature of these new technological possibilities they impact on how governmental institutions and public health international organizations like the WHO can (and should) respond to the threat posed by the life sciences today.

Bringing old (and new) diseases back to life not only raises additional concerns for public health and biosecurity but also calls into question existing definitions and understanding of the concept of emerging infections itself. This possibility also challenges the possibility of establishing a list of select agents on the basis of their genetic sequence (because they can be modified). In his original article on the concept, in which he distinguished five historical situations where a disease can be classified as emergent, Mirko Grmek (1993) carefully added a sub-category that is now gaining currency:

[154] The field of "synthetic genomics" is defined as a combination of various experimental practices and methods to chemically analyze DNA with computer modeling that permits to redesign the DNA sequences. Synthetic genomics thus "could be used to introduce a cumulative series of changes that dramatically alter an organism's function, or to construct very long strand of genetic material that could serve as the entire genome of a virus or, some time in the near future, even of more complex organisms such as bacteria" (Garfinkel, Endy, Epsin, and Friedman 2007, 7).

artificially or manmade emerging diseases resulting from dual-use technologies. According to Grmek, the category of wholly new diseases, in the strong sense of the word, includes the adaptive transformation of germs from saprophyte or commensal organisms into harmful parasitism, and important environmental changes. Grmek added further, however, that

> We could envisage the *theoretical* possibility of an artificially produced disease emerging either as the result of an intended action (for instance, in view of *biological warfare*), or as an *undesirable accident* that occurred in the course of biotechnological manipulations. This would be a *sub-category* of the larger category of absolutely new diseases (1993, 285; emphasis added).

In the last decade, the possibility of engineering disease from scratch has become a pressing social and political issue and is no longer just a "theoretical possibility". In effect, during the past ten years virologists and microbiologists provided strong evidence that with genomic sequences of a number of extinct diseases scientists could bring those diseases back to life, so to speak, and that wholly new virulent ones could be artificially created as well, like in Fouchier's experiment with influenza viruses. The additional category of emergence suggested by Grmek twenty years ago is useful because it highlights the need to readjust our definition(s) of the concept of emerging diseases (or emerging infections) to include man-made diseases. Furthermore, it re-emphasizes the *potentia* dimension of the concept. Finally, this perspective on the possibility to create emerging diseases calls for the development of more appropriate governance responses to this new form of biological threat. By re-aligning the active concept of emerging disease with those issues we may hope that the international organizations will respond promptly as they did fifteen years ago when they economically and politically rebranded the category of communicable diseases as emerging infections.

RINGING THE ALARM: MOUSEPOX, POLIO, SMALLPOX, AND THE 1918 INFLUENZA STRAIN

Prior to 2005, three articles gathered a fair bit of scientific, political, and public attention because they generated controversy over the highly sensitive nature of the reported findings and their possible consequences for public health and for biosecurity: these articles had potential for what is now called "dual-use research" (Selgelid 2009). The first one, published in 2001 in *The Journal of Virology*, reports how a team of researchers constructed an extremely lethal poxvirus in mice. Inserting the gene for interleukin-4 (Il4) into the mousepox virus using genetic engineering techniques, researchers were hoping to develop a way to control the pest in Australia by making the mice infertile.[155] To their own surprise, however, the Australian team discovered that the virus was not only lethal to naturally resistant mice but also to previously vaccinated ones (Jackson et al. 2001). In other words, they had accidentally fabricated a virulent disease able to overcome vaccinated and naturally-resistant mice. Immunological protection granted by vaccination is thus undermined by the possibility of creating viruses capable to infect and cause disease in previously vaccinated or immune organisms. A similar technique could technically permit the development of hypervirulent strains of smallpox (for which there is no treatment) and cricumvent vaccination which so far is the sole line of defense against it (Selgelid 2003).

The second article, published a year later in *Science* (Cello, Paul, and Wimmer 2002), concerns the chemical synthesis of the polio virus in the absence of any natural viral sample. The research was carried out at the State University of New York at Stony Brookes where the team chemically reconstructed a DNA sequence by assembling oligonucleotides and following the instruction of the DNA sequence of the virus that was available on the internet, thanks to prior sequencing and mapping of its genome. This artificially-made DNA strand was then inserted into a living cell where RNA polymerase transcribed the cDNA sequence. The DNA sequence further started to replicate itself, resulting in a virulent phenotype typical of polio virus. This cascade of *in vivo* and *in vitro* macromolecular events was possible without researchers using any viral material. Researchers claimed to have accomplished this achievement "to send a warning that

[155] Ronald Jackson, the principal investigator, was in the late 1980s on a project aiming at enhancing myxomatosis.

terrorists might be able to make biological weapons without obtaining a natural virus" (Pollack 2002, in Selgelid 2009, 721). This experiment, however, raises question regarding the polio vaccination campaigns aimed at eradicating the disease. While the number of vaccinated people globally increases thanks to international efforts, the disease cannot in principle be totally eradicated because it could eventually be re-generated anew, and re-emerge. A recent U.S. report titled *Sequence-Based Classification for Select Agents: a Brighter Line*, led by microbiologist Stanley Falkow, arrived at the same conclusion, namely that "it is possible that no virus (or microorganism) can ever be considered extinct […] as long as basic sequence information is available to support its synthetic reconstruction" (2010, 66). As a consequence if polio is one day declared eradicated, governmental and public health efforts to control or prevent it (e.g. vaccination) would nevertheless have to continue in case of artificial re-emergence.

Finally, the third article (Rosengard, Liu, Nie, and Jimenez 2002) deals with smallpox, the only successfully eradicated human disease in 1977. Nowadays, *in vivo* experiments with variola, the organism that causes smallpox, are forbidden by international law, and samples of the disease are well kept by both U.S. and Russian governments although it is likely that other governments have since learned how to cultivate the organism (Selgelid 2003). WHO also bans DNA recombination studies between variola and other pox viruses. However, scientists report in this article on how they successfully engineered a variola protein which is a crucial virulence factor in the overall pathogenesis mechanism of smallpox. More precisely, they "molecularly engineered" the "smallpox inhibitor of complement enzymes" – or SPICE – and demonstrated the links between this protein and the specificity of smallpox to human tropism. In brief, even if smallpox is eradicated it remains possible to recreate the proteins that contributed to make it so deadly. The authors emphasized that this research is crucial for public health purposes as disabling SPICE protein mechanism could be a fruitful way to treat smallpox.

As a consequence of these new experimental possibilities, however, the perceived biosecurity threat of emerging diseases – once understood mainly as the result of the introduction of a new select agent in a population, a newly detected, but already existing microbe, or as an important change in the environment (Lederberg, Shope, Oaks, 1992, 34) – should be re-worked to include the artificial creation of pathogenic agents, as

Grmek already suggested nearly twenty years ago. This new form of biological threat results from combining the tools of synthetic biology and genomics science. Both approaches, indeed, are crucial to firstly identify and sequence the particular genes responsible for the virulence of the disease inside the pathogen's genome (genomics), and secondly to synthetically recreate and complete the (often incomplete) genetic sequence of the virus in laboratory (synthetic biology). Charles Nicolle once commented that "no scientist can today pretend to have created a wholly new disease from scratch" (Nicolle 1930, 122). This view is now on the verge of being challenged on both theoretical and practical grounds, as the 2006 report of the NSABB indicates, throwing into disarray the current legislation system to control the production and proliferation of dangerous pathogens.

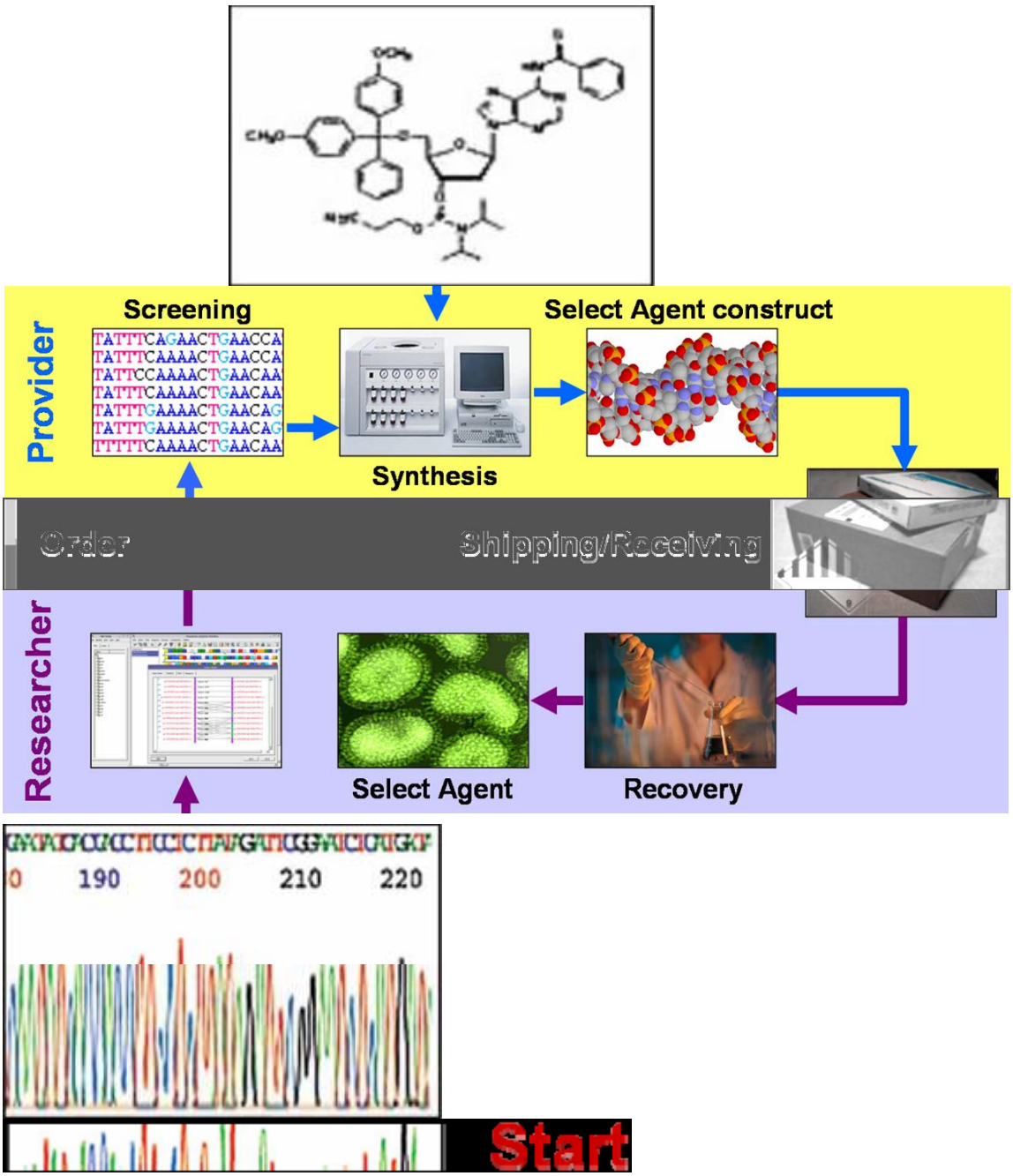

Fig. 7. Process for Deriving Select Agents De Novo Using Mail-Ordered DNA. The relevant sequence is first identified by the research team and is then ordered to a provider who will synthesize it. One the select agent is reconstructed it is sent back to the research team who can culture it (From NSABB 2006, 19).

In the remainder of this section I report and comment on the discussion that took place in the journal *Science* regarding the safety issues raised by the publication of Taubenberger's article on 1918 influenza. Drawing on the work of former member of the Sunshine Project (an organization dedicated to global surveillance of biological warfare in the U.S. and in Europe) Jan van Aken, this section also introduces some fundamental ethical questions concerning the relevance, from a public health perspective, of Taubenberger and similar research projects.

RECONSTRUCTING THE 1918 INFLUENZA STRAIN: AN EXAMPLE OF DUAL-USE RESEARCH

The publication of the whole sequence of the 1918 strain in 2005 sparked lively debates among scientists and raised concerns as to whether it is safe to publish the receipe that was used to resurrect such a deadly pathogen. Upon releasing the complete sequence (and methodology) used to reconstruct the virus in the prestigious journals *Nature* and *Science* discussions took place among scientists and journal editors regarding how safe it was to publish these sensitive data: What if someone with nefarious intentions reconstruct the virus? How likely is it that this genetic information be used for harmful purposes? What if, by accident or not, the virus escapes into the environment? As biologist Richard H. Ebright from Rutgers University said "there is a risk, verging on inevitability, of accidental release of the virus" but "there is also a risk of deliberate release of the virus". For Ebright, the 1918 flu virus "is perhaps the most effective bioweapons agent ever known".[156]

Yet others argued that the work of Taubenberger and Tumpey was entirely legitimate and well-founded as it could be applied to other areas and problems in virology such as the N5N1 pandemic. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases in the U.S., and Julie Gerberding, head of the Center for Disease Control and Prevention (CDC), in a joint-statement, agreed that "the new studies [of Taubenberger and Tumpey] could have an immediate impact by helping scientists focus on detecting changes in the evolving H5N1 virus that might make widespread

[156] From *New York Times* article by Gina Kolata (2005) which can be accessed at http://www.nytimes.com/2005/10/06/health/06flu.html?pagewanted=all

transmission among humans more likely". [157] The case of the Spanish influenza pandemic is today a text-book example of a technique which has the potential for "dual-use" research as the result can either help to understand the disease and fight it, but it also could be used to disseminate it further (Rappert 2007, 3). This example of dual-use technologies and the often-expressed fears of misuse of scientific research by terrorists should be understood in the context of post-9/11 and anthrax attack on the U.S. territory.

THE *SCIENCE* SAFETY REVIEW

The publication of the article "Characterization of the reconstructed 1918 Spanish influenza pandemic virus" by T. Tumpey et al. in *Science* in October 2005 came out with a short Editorial note by Philip A. Sharp from MIT – "1918 flu and responsible science" (Sharp 2005). As the title suggests, Sharp claimed that the research published by Tumpey et al. was a piece of good, responsible scientific work. Addressing the possibility that terrorist groups come into possession of knowledge enabling them them to instigate a pandemic, Sharp dismissed it as very unlikely, however. According to him it is, on the contrary, "reassuring" that the National Science Advisory Board for Biosecurity (NSABB), a government body created in 2003, was asked to consider these papers prior to publication. Furthermore, the committee concluded that "the scientific benefit of the future use of this information far outweighs the potential risk of misuse". Thus, Sharp continues, the decision to publish the paper was made in consultation with agencies representing the public, the journal (i.e. *Science*) and the scientific community.

For, according to Sharp, not only the work of Tumpey and his colleagues made a fundamental contribution to the mechanism of pathogenicity but this research was done according to the safety rules that apply in such situation (i.e. the experiments were conducted in a Biosafety Level 3 laboratory). Overall, Sharp argued that the decision of publishing the article, despite the sensitive nature of its findings, was the right decision. For him, it not only has the potential to "stimulate" further research into this and other

[157] This statement was jointly issued by Fauci and Gerberding. See Kolata (2005).

areas but can also lead to the development of new drugs and the prevention of future pandemics. In brief, “the system is working”.

The reassuring and politically correct response given by Sharp contrasted sharply with the almost challenging tone of the Editor-in-chief of *Science* that appeared in an editorial one week later, on the 14th of October (Kennedy 2005). Filling the gap in the history of the publication of the sensitive article of the 1918 strain, Kennedy began by recalling the creation of NSABB following the recommendation of Gerald Fink in 2003. Like Sharp, he reported that this board was consulted prior to the publication of Tumpey et al. and that its members “voted unanimously in favor of publication”. (The way the NSABB got involved is explained in more detail below). Moreover, prior consultations on the nature of the material in the article were made with Anthony Fauci and Julie Gerberding. Amy Patterson, head of the Office of Biotechnology Activities, was also informed of the planned publication. “All three felt that the public health benefits of the study far outweighed any biosecurity risks”, Kennedy reports.

And yet, on the 27th of September, one day before the article and the whole issue was going to go off to print, the Office of the Secretary of the U.S. Department of Health and Human Services (HHS) informed the editors of *Science* that they had concerns about the publication of the article and asked for a second safety review. The HHS Secretary Michael Leavitt argued that the NSABB should review the paper to ensure its publication does not endanger public health. The review committee was quickly organized and they reviewed the paper within a day. The NSABB review was thus a very last-minute operation, not something planned long ahead, or part of a normal review process. The committee suggested two things: firstly, to add an editorial addressing a number of ethical and safety issues arising from the publication (this was done by P.A. Sharp); and secondly, the committee asked the editors to add a note on the paper to highlight the safety of the scientific procedures and the potential benefits in terms of public health.[158] Although the paper was judged appropriate to go to print, the editor-in-chief was not

[158] The note added in proof says “The research was done by staff taking antiviral prophylaxis and using stringent biosafety precautions to protect the researchers, the environment, and the public. The fundamental purpose of this work was to provide information critical to protect public health and to develop measures effectives against future influenza pandemics” (Tumpey et al. 2005, 80).

happy with the decision of the HHS to review it once again, especially on such short notice and after other positive reviews by competent scientists. Kennedy also reminded the NSABB that their mandate is to provide guidelines, not to "screen individual papers". The last minute intervention of the NSABB was later explained to the editors to be intended as a practical exercise on a "live" issue.

But all this is somewhat beside the fundamental point that was raised by the NSABB review. As Kennedy pointed out "there is a real question of authority here". In other words, who should police the scientists? Who should decide whether an article should be published or classified? With the current system into place there is no other alternative to either publish or classify an article. And no scientific article, so far, is known to have been denied publication for reasons related to biosecurity (Aken 2006, 10). In his editorial Kennedy was adamant that government and science are distinct bodies and that while the former can inform the latter – emphasizing that scientists would be "wise" to listen to those recommendations – government agents, however, should not directly interfere with the review process of scientific publication. In a somewhat defiant tone, Kennedy concluded asking whether *Science* would have published the paper if the NSABB had voted differently. His response was "absolutely – unless they had it classified". [159] This indicates that the current measures to control and assess the publication of sensitive findings in the life sciences are inadequate. For one thing, they conflict with scientific autononomy, a value often branded as essential to scientific research itself.

Nature also published a sensitive paper on influenza in 2005. In "Characterization of the 1918 influenza polymerase genes" (2005) Taubenberger and his team published the sequence of the last three genes of the virus, providing thus a full and complete sequence of the deadly pathogen that killed millions of people worldwide in 1918 and 1919. The responses in *Nature* were more polarized than in the case of Science, and although some scientists openly considered that the paper should not be published, no one suggested

[159] According to Peter Galison the amount of classified science in the U.S. is five to ten times larger than the open scientific literature (2004, 231). In the U.S. only, 4000 people – called *Original Classifiers* – can transform documents, pictures, graphs, equation from the realm of publicly accessible research objects to the "classified universe". The amount of classified knowledge just mentioned, however, does not include research which does not require a classification act, for instance nuclear knowledge which is "born" classified, as it were (Ibid).

that the research should not have been undertaken from the outset. [160] Following the publication of the article the virus of the 1918 influenza pandemic was, however, immediately classified as a select agent by the Department of Health and Human Services and the Center for Disease Control and Prevention. This legislation, amended by Michael Leavitt, renders "any portion of the coding regions of all eight gene segment" subject to strict regulation regarding use, possession, and transfer. The document added that "the apparent virulence of this virus, together with the fact that the level of immunity in the general population and the ability of the virus to readily transmit among persons are unknown at this time, makes it prudent to immediately regulate this virus as a select agent", despite its potential benefit in terms of fundamental research and vaccines development (Federal Register 2005).

As sociologist Brian Rappert (2007) reports, the discourse behind the official scientific scene was somewhat different and raised new questions that did not emerge so sharply during the discussion between editors, scientists and government officers. For instance, in contrast with those who voiced concerns about the publication of the results, the members of the Sunshine Project asked whether it was wise to conduct this research in the first place (Aken 2006).[161] According to Aken the debate on whether or not to publish sensitive data is necessary despite that it leaves out the deeper issue of what kind of science should be funded and promoted. Questioning the scientific justification of the project and its potential benefits in terms of prevention altogether, Aken argues that a cost-benefits analysis reveals important flaws in the 1918 influenza research, blurring at the same time the line between the development of bioweapons and biomedical research.

According to Aken, while the costs of such project can (and have been) readily be identified, the benefits are much harder to discern. Costs include the possibility for rogue scientists to recreate the virus and the risk to see yet another influenza pandemic in

[160] For an analysis of the *Nature* reports see Rappert (2007).

[161] This NGO, though perhaps not that visible, was not however as marginalized as what Rappert appears to say. In fact, one of the members published a piece in 2006 in the European Molecular Biology Organization (EMBO) reports (Aken 2006).

populations now wholly susceptible, and the possibility for the virus to escape laboratories and contaminate the environment. As we have seen in this chapter, reconstructing the 1918 strain of influenza was predicated (and largely funded) on the possibility of identifying the genes responsible for its extreme pathogenicity, and on the hope that this deeper molecular understanding of virulence factors could lead to the development of vaccines designed to protect public health in case of future influenza pandemic. The first goal of the project (identifying virulence genes in the 1918 sequence) was not reached and the second is always in progress because although influenza vaccines exist, the capacity for influenza A viruses to mutate at a rapid pace hampers the development of long-term vaccination efforts. Moreover, although inactivated vaccines could be made readily available in several developed countries following the outset of an influenza pandemic, the stocks are not however unlimited (Webby and Webster. 2003). It is often stressed that identifying those factors of virulence would further allow predicting the occurrence of future pandemics, also contributing to public health protection (von Bubnoff 2005).

Those arguments in terms of public health benefits are, however, too general to counterbalance the costs of the influenza project in terms of biosecurity (Aken 2006). Indeed, it is virtually true of every scientific research in biomedicine that the outcomes will somehow provide a better understanding of a particular disease. Thus, cost-benefit analysis should ask more specific question like: is this project addressing a genuine public health problem? Could the problem be addressed and investigated differently? What are the alternatives to recreating the 1918 Spanish flu strain to understand influenza pandemics? Indeed, research on influenza viruses can be done (and indeed, is done) on other strains than the 1918 one. The existence of the Influenza Genome Project facilitated the sequencing of a number of influenza strains, some more virulent than others, so why sequencing the 1918 one, knowing that serious risks for both public health and biosecurity are associated with it? This question concerns not only levels of biosecurity but underlines the fact that scientists sometimes secure massive amount of funding over long periods of years based on rather vague claims and promises about possible benefits in terms of health improvement or the development of new treatments.

CONCLUDING REMARKS

The Sunshine Project report concluded that the global and individual benefits of such research remain, so far, unclear. Moreover, they think we are at greater risk of experiencing an influenza pandemic now that the virus has been recreated. For them, there was "no valid reason to recreate the virulent virus, as the risks far outweighs the benefits" (2003, in Rappert 2007, 6). The Sunshine Project report also claimed that the reconstruction of the Spanish influenza virus, a technological achievement in itself, was primarily carried out not for nefarious reasons or to find new treatment but *because* it was technologically possible to do it: "It appears that this work was not triggered by a search for flu treatments, or the serach for new biowarfare agent, but by a rather simple motivation: Taubenberger and his team were just able to do it. In previous experiments they had developed a new technique to analyse DNA in old, preserved tissues and were now looking for new applications" (2003, in Rappert 2007, 6). In other words, according to the Sunshine Project reports, a powerful technological determinism has led Taubenberger and its team into reconstructing the strain of influenza virus that killed millions of people worldwide. While this is certainly part of the explanation, there is also a historical reason here that needs to be emphasized here. Looked at from a *longue durée* history standpoint, the research undertaken by Taubenberger epitomizes the end point of a wider reductionist research program (or style) in the life sciences which has attempted to uncover the nature of virulence by looking always deeper within pathogens – tissues, cells, genes, and genome – in the hope to discover the source of disease power they too often display. The available technology enabled the researchers to carry out a project otherwise impossible. However, one should be careful in attributing responsibility only to the technology being available in the development of the project. The experiments of Taubenberger and others are part of a larger picture which should not be ignored.

The concept of emerging disease should be rebranded anew to include manmade artificial diseases. As this concept is able to lever economical and political powers it could be helpful to use it to call attention to those new threats posed by the life sciences. While it might be said that dual-use is a characteristic of most life sciences nowadays (Atlas 2009), only a small number of experiments and experimental practices are, overall, seen as posing real threats to public health and global security. In addition, dual-use

technologies are often characterized by unexpected findings such as, for instance, the accidental discovery that a modified virus injected in mice was lethal to otherwise vaccinated animals. This case can be regarded as an example of what Grmek called an "undesirable accident", not only because the publication of these findings provided instructions as to how to create a highly virulent virus, and this information is now publicly available to anyone, but because the results were unforeseen. As if often the case in research, the experimental system designed to answer certain questions opens-up new possibilities that could simply not be envisaged at the outset (Rheinberger 1997). If unpredictability is truly the essence of scientific research, dual-use technologies are an unavoidable trade-off to deal with. This epistemic dimension of scientific research reinforces the need to develop appropriate governance responses to biomedical research on pathogens and potentially pathogenic organisms. More generally, it underlines the need for the development of a "sociology of virulence" (Van Loon 2002), a "culture of responsibility" (NSABB 2011) in the life sciences, that is, a new *ethos* to address questions of security, risk and scientific autonomy, among others. The intricacy of power and knowledge is well reflected in the biomedical concept of virulence whose effects is not contained within the walls of the laboratories but translates at several levels and foster changes in both discourses and practices in the biomedical sciences.

GENERAL CONCLUSION

The historian of biology and Nobel Prize laureate François Jacob once remarked that there are two approaches to the history of science. According to Jacob, the history of science

> may be considered as a succession of ideas, thus involving a search for the thread which guided thought along the path to current theories. This is reverse history, so to speak, which moves back from the present towards the past. Step by step, the forerunner of the current hypothesis is chosen, then the forerunner of the forerunner, and so on [...].

Yet this is just one possible option. An alternative approach

> involves the attempt to discover how objects become accessible to investigation thus permitting new fields of science to be developed. It requires analysis of the nature of these objects, and of the attitude of the investigators, their methods of observation, and the obstacles raised by their cultural background. The importance of a concept is defined operationally in terms of its role in directing observation and experience. There is no longer a more or less linear sequence of ideas, each produced from its predecessor, but instead a domain which thought strives to explore, where it seeks to establish order and attempts to construct a world of abstract relationships in harmony not only with observations and techniques, but also with current practices, values and interpretations (Jacob 1973, 11).

The second part of the quote summarizes well what was attempted here: to follow the intertwined emergence of research objects and investigative techniques through a particular form of scientific practice: the formation of concepts. I argued that a history of concepts, informed by the philosophical method of Georges Canguilhem and other historical epistemologists, is promising in terms of an integrated approach to the history and philosophy of science. Building on a new interpretation of operational analysis, I challenged the claim that concepts are inadequate units of narration and analysis. Against the interpretation that concepts are "products", i.e., static things, I endeavoured to show that, on the contrary, concepts are evolving, morphing, and especially acting entities. Concepts are not innocent; they do not just *represent*, they also *intervene* in the outside

world, to use Hacking's words (1983). For instance, they direct "observation and experience" (Jacob 1973, 11) and in this respect, they significantly contribute in shaping the process of scientific research and the growth of knowledge. Looking at virulence as a concept in action provided new ways of interpreting the development of important episodes of the past's century biomedicine and their broader significance from a *longue durée* standpoint. We have seen, for example, how the problem of changes in virulence in Griffith's experiment has triggered a fifteen years long search for the material basis of virulence which culminated in the (unforeseen) discovery that genes are made of DNA. Particularly so in the life sciences, also, concepts are crucial operators around which disciplines, knowledge, practices, discourses, and evaluations become established.

In turn, this approach to concepts headed not into a "linear sequence of ideas" or "reverse history" but rather into the examination of the formation of a broad domain of research, or as Staffan Müller-Wille and Hans-Jörg Rheinberger have called it, an "epistemic space" (2007, 3). Maybe not unlike the concept of heredity (Gayon 2000), the concept of virulence could interestingly be characterized as being either an operationalized magnitude (or force) or as a structure. However, in the case of virulence (unlike heredity) the two conceptions developed alongside parallel lines and did not undergo a sharp shift from one another. But this is a topic that would deserve more space than what can be given in a conclusion. Likewise, though, to map out the contours and the place of virulence at different points within contemporary biomedical sciences, it has been necessary to investigate a number of apparently disconnected fields, often not related in any obvious ways.

Following the investigation of several of these fields, the present work brings out in a new light the importance given to the nature of infection as part of our scientific discourses and practices during the past two centuries. And within this epistemic space, I examined two of the main roads that were developed in exploring this conceptual domain: the exogenous and the endogenous styles. Following the development of those styles, we have seen how each of them "opened-up new territory" to use Hacking's words again (1992, 8). The formation of those fields, where "thought strives to explore" as Jacob put it, allowed for distinctly new concepts, practices and problems to come into view.

What is emerging at the end of this journey, underneath the concept of virulence so to speak, is the wider problem of inter-species relations, or parasitism, in shaping states of health and illness. As philosopher Michel Serres wrote several years ago, the introduction of a parasite within a system is always destabilizing: it "provokes a difference, disequilibrium" (1982, 182). Following the course of infection, while organisms attempt to restore their lost equilibrium (or to create a new one), the parasite either becomes adapted or is destroyed by the host in which it provoked a big or a small physiological difference we call illness or health. Parasitism is part of the natural order of things although this order is never given once and for all. Indeed, "the parasite is an exciter" (Serres 1982, 191). The concept of "evolving parasitism" as coined by Theobald Smith can be seen as an attempt to come to terms with the ecological dynamics of host and parasite's relations, and with the existence of diseases as natural phenomena. The optimism in the "law of declining virulence" reflects the hope of undermining the dynamics of the parasite, or at least to momentarily escape this logic of constant destabilizations. Smith, Burnet and many others who, likewise, were seduced by this evolutionarily attractive hypothesis knew, however, that this logic holds only in cases of unchanging environments. Yet this was an unrealistic assumption for, as the natural world is always subject to change, so are its inhabitants. Since environments and organisms fluctuate, the parasite keeps on introducing differences within previously established physiological orders. Homeostasis, the conquest of equilibrium, is always precarious.

Other concepts endeavouring to locate the cause of infection deep inside certain structures in organisms belonging to certain species mirror a comparable attitude before the parasite, namely the desire to place order onto the natural world. Following Koch, only some living things are endowed with pathogenic powers; and following Pasteur health is, for an organism, synonymous with being germ-free. In both cases infection is ruled out as pathological, as abnormal. The parasite is like an intruder in natural history. Attempting to address the nature of parasitic infection one-sidedly, this logic culminated with the molecularization of Koch's postulates and the search for an utter difference between pathogenic and non-pathogenic organisms at the level of the genome. Sharpening the distinction between what is and what is not parasitic (and hence, normal and pathological) in absolute terms, however, is to erect conceptual barriers that are

estranged to the nature of the parasite. As a permanent difference-maker, the parasite disturbs sometimes long-established equilibriums, for example in moving freely between phylogenetically distant organisms. Provided that we think of the phenomenon of parasitism in broad enough terms we can see that the transfer of pathogenicity islands, able to transform a previously benign organism into a wholly pathogenic one, is one such example. The process of species evolution by association (Sapp 1994) could itself be interpreted as a series of perpetual conquest of imbalances within distinct biological systems resulting from the introduction of parasitic intruders. Biological adaptation is a ramified process that can work in "quantum leap" (Groisman and Ochman 1996).

From 1880 until the present, the problem infection was most of the time addressed as coming either from outside or from within organisms. It is plain, however, that the frontier between what is inside and what is outside is relative. The inside of a cell is the outside of its intra-cellular elements. An organism is a complex ecological site, itself situated in a wider milieu. Similarly, individuality is not a being; it is a mobile relation, as Canguilhem stressed (2008 [1952]). Ascertaining particulars ways over others to address the problem of infection, the concepts developed within the two styles are the result of looking at virulence inwardly or outwardly. Those gazes finally met briefly in the mid-1990s during the aftermath of a crisis triggered by what appeared to be a wholly new disease: AIDS. Facilitated by the concept of emerging disease, and motivated by the growing fears of a world "out of balance" (Garrett 1994), the two styles were drawn together. At last, infection was addressed *at the same time* both as an external (ecological) and an internal (molecular, genetic) problem, and their relation.

From a historical point of view, this convergence between styles thanks to the concept of emerging disease, allowed completing a shift instigated in the nineteenth century in the concept of "new disease". In effect, this concept wrapped up a much earlier attempt to see the living world as one dominated by change, not stasis. This shift was called for in pathology by Charles Boersch in 1836 who wrote:

> There are animal and plant races which no longer exist in their primitive form; each day, art, education, and civilisation transform animal and plants living with us. Why would it be different in the case of diseases? Why could there not be historical diseases, just like there are fossils of plants and animal? (Boersch 1836, 96 quoted in Anglada 1869, 33).

While including plants and higher organisms within an evolutionary framework was successfully achieved by the first half of the twentieth century (symbiosis aside; Sapp 1994), bacteria and other disease agents continued to stand uneasily outside the Modern Synthesis framework as more or less static entities, or at least as relatively unchanging ones (see Snowden 2008).[162] By being more inclusive towards the microbial world and by looking at diseases from an evolutionary lens, it became possible in the mid-1990s to make sense of historical diseases, that is, to think about emerging diseases dynamically. Breaking with traditional views about microorganisms, the recent convergence between styles also indicates the acknowledgement, from different perspectives, that the microbial world is not static but is "full of potential and surprise" (Weir and Mykhalovski 2010, 62). In a "world on alert" (Ibid.), the need for broader and wider surveillance and detection systems to monitor emerging diseases grows stronger. In light of the pathological possibilities contained within the microbial world that can be unleashed through human activities as well as from other forms of evolutionary changes microorganisms naturally undergo, the concept of "forward looking" evolutionary explanation (chapter 2), as intended to capture the idea that disease agents are things that are still evolving, is most significant. As Lederberg long indicated, we can read the history of epidemics as "one of the last refuges of the concept of special creationism, with scant attention to dynamic change on the parts of the agents of disease" (1993, 3). Furthermore, it is conceivable that the concept of emerging disease could bring Darwinian and evolutionary medicine closer to one another. For instance, the etiology of a number of chronic diseases (disease of evolution) turns out be the result of evolutionarily changes in infectious agents (evolution of disease), as the cases of peptic ulcer and human papilloma virus-caused cancer exemplify. These evolutionary perspectives on disease may

[162] These views about the fixity of the mircobial world during the twentieth century will require further research.

well be two sides of the same coin. Then again, practitioners in each category have distinct commitments as to how best approach medicine from an evolutionary standpoint. At any rate, the development of the two styles also allows revising the claim that there was little articulation between evolutionary biology and medicine until the dawn of Darwinian medicine in the 1990s. On the contrary, such encounters have frequently occurred and evolutionary thinking supported some of the most influential models of disease evolution.

Stepping back, the persistence of the two approaches to virulence throughout the twentieth century invites reflection. Knowing that explanations of virulence took two different forms for decades (even centuries), it hardly comes as a surprise that scientific explanations of the 1918-19 pandemic reflect this ancient dichotomy. Bearing this in mind, it becomes clearer why both reductionist and environmental-driven styles continue to being developed in a relatively independent fashion to one another. These styles, however, are not genuinely new but are instead the result of older and deeper trends in the history of the life sciences. In fact, the discontinuity between these different styles reflects slow and deep historical movements, the shifts from one of these approaches to another being the result of history that "unfolds slowly and is slow to alter, often repeating itself and working itself out in cycles which are endlessly renewed", to quote the historian Fernand Braudel (1980, 3). This *longue durée* perspective also sheds new light on the ethical issues raised by the reconstruction of the 1918-19 strain of influenza. This project of recreating potentially dangerous organisms, coming into sight in the late 1990s, does not merely reflect newly developed practical possibilities but caps a much longer research tradition within the endogenous style where infection is conceptualized in reductionist terms.

The structuring role and the centrality of the concept of virulence in today's health sciences are, to some extent, truly surprising, however. Why do scientists continue to use this centuries-old concept? Perhaps the concept of virulence is still in use because it allows scientists to maintain previously established terms and facilitates communication among them. Understood in this way, the concept of virulence persists for pragmatic reasons alone. It may be, however, that it persists because the "theme" of infection is one of those that Georges Canguilhem once said "are few in numbers" and "come from far

away". Such themes, he continues, "survive the apparent destruction that polemics and refutations pride themselves in having wrought" (2008, 56 [1952]). These "ancient images", as Canguilhem put it, or "proto-ideas", to use Ludwig Fleck's vocabulary, become deeply entrenched in scientific practices to the extent that it becomes virtually impossible to let them go or replace them. These concepts and themes are crucial as they provide continuity with the past of a science while at the same time establish wider connections with social and political concerns.

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