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Biomedicine: Meanings, assumptions, and possible futures

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Report to the Swiss Science and Innovation Council (SSIC)

Préface du Conseil suisse de la science et de l'innovation

Le Conseil suisse de la science et de l'innovation (CSSI) a défini au sein de son programme de travail 2012–2015 un projet intitulé «Tendances de la recherche en biomédecine». Dans ce cadre, il analyse les développements récents de ce domaine scientifique hybride d'une importance majeure pour la Suisse, et réfléchit à leurs implications pour l'organisation de la recherche publique et privée. Le projet se concentre sur les questions propres à la recherche, tout en prenant en compte les principales interfaces de la formation, de la santé et de l'innovation.

Dans un premier temps, le CSSI a mandaté deux études originales interrogeant la notion de biomédecine ou de recherche biomédicale. La première, présentée dans le présent rapport, retrace l'évolution de la biomédecine en tant que nouvelle discipline épistémologique depuis les débuts du 20ème siècle jusqu'à nos jours. Une deuxième étude explore le paysage suisse de la recherche biomédicale sous l'angle du discours des acteurs institutionnels et des chercheurs individuels[1]. Ces différents travaux, qui éclairent le domaine biomédical selon des perspectives complémentaires, sont aujourd'hui publiés en parallèle sous la responsabilité de leurs auteurs respectifs.

Dans un deuxième temps, se basant sur les résultats de ces études ainsi que sur les réflexions d'autres acteurs institutionnels, le CSSI va formuler des thèses et recommandations relatives aux enjeux liés à la recherche biomédicale en Suisse.

1 Benninghoff, Martin, Ramuz, Raphaël, and Lutz, Andrea. 2014. *La recherche biomédicale en Suisse: espace social, discours et pratiques*. Berne: Document CSSI 2/2014.

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Biomedicine: Meanings, assumptions, and possible futures

At the beginning of the twentieth-century work in biomedicine was a small area of activity within medicine. Today, biomedicine is a major engine for both medical progress and economic growth as well as an integral part of how health, illness, and individual identity are understood. However, the foundations of biomedicine are in the midst of a great transformation, a transformation with profound implications for medicine, research, commerce, and public policy. This report presents a discussion and analysis of biomedicine to inform the deliberations of policymakers as they address these contemporary changes.

— Biomedical research is a unique way of understanding health and illness, based on the investigation of biological mechanisms, the use of the randomized clinical trial, and the identification and quantification of disease risks.
— Biomedical research rests upon three powerful assumptions—universalism, reductionism, and modelization—which are currently being challenged by the results of biomedical research itself.
— The history of biomedicine produced by biomedical researchers does not reflect the actual process of biomedical innovation; it underestimates the complexity of therapeutic development, the importance of clinical and industrial research, and the role of state and other public actors.
— The development of biomedicine has been powerfully shaped by state policy, but in the twenty-first century a new set of relevant actors is emerging, including patient organizations, start-up companies, and non-profit pharmaceutical industries.

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La biomédecine: significations, prémisses et perspectives[2]

Au début du 20ème siècle, la recherche biomédicale ne constituait qu'un modeste domaine d'activité au sein de la recherche médicale. De nos jours, la biomédecine est un vecteur capital du progrès médical comme de la croissance économique, et elle fait partie intégrante de notre compréhension de la santé, de la maladie et de l'identité individuelle. Toutefois, les fondements mêmes de la biomédecine sont actuellement remis en question, et ce bouleversement a d'importantes conséquences sur la médecine, la recherche, l'économie et les politiques publiques. Le présent rapport propose une discussion et une analyse des enjeux liés à la biomédecine, afin de fournir des bases de réflexion aux acteurs politiques en prise avec ces changements.

— La recherche biomédicale développe une approche unique pour appréhender la maladie et la santé, basée sur l'étude de mécanismes biologiques, sur le recours à des essais cliniques randomisés ainsi que sur l'identification et la quantification des risques de maladie.
— La recherche biomédicale repose sur trois prémisses principales – universalisme, réductionnisme et modélisation – qui sont actuellement remises en question par les résultats de la recherche biomédicale elle-même.
— L'histoire de la biomédecine telle qu'elle a été décrite par les chercheurs de ce domaine ne reflète pas le processus effectif de l'innovation biomédicale; elle sous-estime la complexité du développement thérapeutique, l'importance de la recherche clinique et industrielle, ainsi que le rôle de l'Etat et des autres acteurs publics.
— Le développement de la biomédecine a été fortement marqué par la politique publique. Toutefois, le 21ème siècle a vu l'émergence de nouveaux acteurs, en particulier des organisations de patients, des start-up et des organisations pharmaceutiques à but non lucratif.

2 Traduction SEFRI.

D

Biomedizin: Bedeutungen, Annahmen und mögliche Perspektiven[3]

Zu Beginn des 20. Jahrhunderts war die biomedizinische Forschung ein kleiner Tätigkeitsbereich innerhalb der Medizin. Heute ist sie ein wichtiger Antrieb, sowohl für den medizinischen Fortschritt als auch für das Wirtschaftswachstum, und ein wesentlicher Bestandteil unserer heutigen Auffassung von Gesundheit, Krankheit und individueller Identität. Die Fundamente der Biomedizin sind allerdings in einem tiefgreifenden Wandel begriffen – einem Wandel mit weitreichenden Auswirkungen für Medizin, Forschung, Wirtschaft und öffentliche Politik. Dieser Bericht enthält eine Diskussion und Analyse der Biomedizin und soll damit den politischen Akteuren, die mit diesen aktuellen Veränderungen umgehen müssen, Entscheidungsgrundlagen liefern.

— Biomedizinische Forschung ist ein einzigartiger Ansatz, Gesundheit und Krankheit zu begreifen, der auf der Untersuchung von biologischen Mechanismen, der Verwendung von randomisierten klinischen Studien und der Identifizierung und Quantifizierung von Krankheitsrisiken beruht.
— Biomedizinische Forschung stützt sich auf drei zentrale Annahmen – Universalismus, Reduktionismus und Modellierung –, die derzeit von den Ergebnissen der biomedizinischen Forschung selbst infrage gestellt werden.
— Die Geschichte der Biomedizin, wie sie von Forschenden, die in diesem Feld selber tätig sind, dargestellt worden ist, reflektiert nicht den eigentlichen Prozess biomedizinischer Innovation; sie unterschätzt die Komplexität der Therapieentwicklung, die Bedeutung klinischer und industrieller Forschung und die Rolle des Staates sowie anderer öffentlicher Akteure.
— Die Entwicklung der Biomedizin wurde stark von der öffentlichen Politik geprägt; im 21. Jahrhundert tritt jedoch eine Reihe zusätzlicher wichtiger Akteure in Erscheinung. Dazu gehören Patientenorganisationen, Start-up-Unternehmen und nicht gewinnorientierte pharmazeutische Organisationen.

3 Übersetzung SBFI.

Intro-duction

"There is no separate science of medicine or physiology, there is only a science of life [...] the true sanctuary of scientific medicine is the laboratory [...] every scientific physician should have, therefore, a physiology laboratory."

Claude Bernard, 1865

"[What is] true of E. coli must also be true of Elephants."

Jacques Monod and François Jacob, 1961

We live in a biomedical era. More now than ever before, how we understand disease, where we seek its cures, and even the ways we conduct our lives depend on the complex system of values, practices, and institutions which define biomedicine. Linking science and medicine, industry and the state, professionals and lay publics, this system had its origins in the late nineteenth century but grew dramatically after the Second World War. It now dominates how Western societies understand and produce knowledge about health and illness. Today, it is undergoing a major transformation with crucial economic, social, and political consequences.

In the midst of this transformation, numerous actors such as the Swiss Science and Innovation Council seek insights for creating a framework favoring the development of biomedicine in a way that will maximize its benefits for society. To understand what might be accomplished, it is important to examine what similar actors have done in past situations. While the study of history may never offer direct prescriptions for future action, it can act as a guide by preventing organizations from promulgating policies based on a misunderstanding of past events and policies. Thankfully, in recent years a number of scholars have started to explore the history of biomedicine. It is thus now possible to draw a synthesis of this work and outline its relevance for public policy. This is what the present report offers.

Biomedicine rests on a specific way of producing knowledge about health and disease: biomedical research. This means of producing knowledge is distinct from any other. Although public debates focus on the capacity of biomedical research to reach the goals it has set for itself, i.e. to cure AIDS or cancer, even at its moments of greatest success biomedical research can only answer the questions it tries to answer. Therefore, it is essential to enlarge our understanding of biomedicine to address it more broadly as a way of knowing: identifying what questions it asks (or ignores) and what it presents as acceptable (or unacceptable) answers to its questions. Biomedicine's questions and answers depend on a set of assumptions about the relationship between science and medicine, health and disease, knowledge and action. Making these assumptions visible and subjecting them to critical analysis grants us greater power to assess the goals of current and future biomedical research. The present report offers a critical overview of the vast scholarship, in the fields of history, philosophy, sociology, and anthropology of science, technology and medicine, about the development and current workings on biomedicine. Biomedicine has changed over time and so has our understanding of it. Yet the way biomedicine is conceptualized today often reflects the past and present goals and ideologies of biomedicine rather than its actual practices. This is why critically assessing the meaning and assumptions behind current biomedical practices is so important: it allows us to move beyond a superficial discourse that is part of (rather than about) biomedicine, and begin to understand the deep transformations that are affecting biomedical research today.

In part one, this report reviews how biomedicine is conceptualized today. It focuses on explicit definitions before turning to how these definitions are embodied in stories about the past successes of biomedicine. It contextualizes the discussion about biomedical research within the changing purview and goals of contemporary medicine. In part two, the report identifies the three fundamental epistemological assumptions of biomedical research before discussing the role of each of its key actors. In part three, the report assesses the possible futures of biomedical research.

Part One

What is biomedicine?

1 Defining biomedicine

The terms "biomedicine" (and "biomedical") have different origins and trajectories in English, German (*"Biomedizin"*), and French (*"biomédecine"*), but very similar meanings today. "Biomedical" first appeared in the writing of American and British authors in the 1920s, followed a decade later by "biomedicine" (or "bio-medicine").[4] The *American Medical Dictionary* (1923) defined it as "clinical medicine based on the principles of physiology and biochemistry", rather than on the "art of healing", or the expertise physicians gained through their practice.[5] Thus, from the onset, biomedicine and biomedical research were understood as a kind of medicine that was closely associated with experimentation and the laboratory rather than doctor's knowledge and the clinic.

1.1 The two meanings of biomedicine

In the 1950s, the term "biomedicine" took on a new meaning, which we will label biomedicine$_2$, and which existed in parallel to its earlier definition, biomedicine$_1$. Biomedicine$_2$ came to designate a kind of medicine studying the *bio*logical effects of extreme environments on the human body.[6] This use was most attached to studies about the biological consequences of radioactive fallout and space travel. This meaning has evolved, especially in German, to designate various kinds of alternative and holistic medical practices (where the "bio" designates not the experimental biological sciences, but an organic whole).

Today, "biomedicine" conserves these two meanings which point, epistemologically and socially, in opposite directions.[7] Biomedicine$_1$ tries to explain the function of the abnormal (pathological) body in terms of normal biological processes, whereas biomedicine$_2$ tries to explain the function of the normal body in abnormal environments. Socially, biomedicine$_1$ is considered "orthodox" or "scientific" medicine and biomedicine$_2$ "alternative" medicine. However, both agree that the difference between the normal and the pathological is one of degree, not of kind. This in itself represents a relatively recent development in the history of medical thought. Physicians such as the famed nineteenth-century German pathologist Rudolf Virchow have long based the autonomy of medicine on the so-called "ontological view" of disease: that disease was the product of specific pathological structures and processes distinct from the healthy functioning of the human body.[8] Yet in the late nineteenth century other physicians, such as French physiologist Claude Bernard, advocated a "physiological view" of disease, where pathology was only a deviation from normal biological processes. Medicine could thus be studied as a subset of physiology and other sciences. As Bernard put it in his *Introduction to Experimental Medicine* (1865) "for a man of science, there is no separate science of medicine or physiology, there is only a science of life [...] the true sanctuary of scientific medicine is the laboratory [...] every scientific physician should have, therefore, a physiology laboratory."[9] Bernard's idea formed the intellectual basis for the project of biomedicine even though, as the philosopher Georges Canguilhem famously pointed out, the reduction of pathology to physiology remained an ever elusive objective rather than a definitive accomplishment.[10]

At present, "biomedical research" is used almost interchangeably with "medical science" or "laboratory medicine", i.e. to designate a form of medical research based on experimentation in the laboratory and framed by knowledge in the natural sciences, such as physiology or bacteriology. This usage corresponds to biomedicine$_1$ as we have discussed it above in that it demarcates biomedicine from clinical research or practice. For the rest of this report, we will focus on biomedicine$_1$, which has become the dominant use of the term by far.

4 Keating & Cambrosio 2003, chapter 3.
5 Dorland 1923.
6 Cambrosio & Keating 2001, p. 1223.
7 *The American Heritage Medical Dictionary* 2013.
8 Temkin 1977.
9 Bernard 1957, pp. 146–147.
10 Canguilhem 1966.

1.2 Biomedicine as modern, molecular, orthodox, and Western medicine

After the Second World War, biomedicine also came to signify "modern medicine" as opposed to a more "traditional medicine" associated with the clinical acumen of individual physicians. Although the laboratory had served as a rallying standard for medical reformers since the late nineteenth century, it was only after 1945 that laboratory-based medicine, or biomedicine, began to have a strong impact on clinical practice.[11] The transformation of medicine into biomedicine was understood as being one of the modernizing projects of Western nations, in which scientific rationality served as a guiding principle. During the mid-twentieth century, this notion of biomedicine as modern medicine came to be associated with two sets of related meanings. First, biomedicine became "molecular medicine", i.e. laboratory research about the role of molecules in health and diseases.[12] Second, biomedicine became synonymous with "Western medicine" (the kind of medicine institutionalized and dominant in Western countries) as contrasted with "non-Western" medicine (the kind of medicine institutionalized in Asian countries for example), "alternative" medicine (the kind of medicine practiced in Western countries but that does not follow the principles of Western science), or "indigenous" medicine (the kind of medicine practiced by healers in communities with belief systems thought to be at variance with Western science).[13]

1.3 Therapeutic innovation in the laboratory

The relationship between laboratory and clinical research is the defining feature of biomedicine. This definition of biomedicine has exerted a profound influence on the institutional, political, and intellectual development of medicine. It has determined not only what kinds of research get funded but what goals and agendas are considered legitimate, even scientific. Biomedicine locates the origin of therapeutic innovation in the laboratory, not the clinic. For example, the present entry for biomedicine in the *Oxford English Dictionary* defines it as: "medicine based on the *application* of the principles of the natural sciences and especially biology and biochemistry."[14] The relationship implied here is clear: discoveries made in the laboratory about the biological nature of disease are then *applied* to the clinic. Under this definition of biomedicine, *all* experimental research on basic biological mechanisms possesses potential relevance to medicine. This argument has been enthusiastically championed by molecular biologists since the mid-twentieth century even though, as historian of medicine Jean-Paul Gaudillière has shown, these laboratory researchers, at least in France, distanced themselves as much as they could from clinical research and practice.[15] The limitations of the distinction between *basic* (laboratory) research and *applied* (clinical) practice are immediately apparent in the case of biomedicine. Indeed, the production of knowledge about therapeutics always involves a clinical phase involving patients, where research and therapy take place at the same time on the same subjects.[16]

The Organisation for Economic Co-operation and Development's (OECD) three-point definition of biomedical research reflects the different perspectives outlined above.[17] The two first points are so broad as to include everything that can be called medical research and development: "the study of specific diseases and conditions" and "the design of methods, drugs, and devices". However, its last point makes the specific claim

11 Warner 1991; Cunningham & Williams 1992; Quirke & Gaudillière 2008.
12 Sinding 1991.
13 Lock & Nguyen 2010, chapter 6.
14 "biomedicine, n.". OED Online. December 2012.
15 Gaudillière 2002.
16 Löwy 1996.
17 OECD 2006.

that biomedical research is "the scientific investigation required to understand the underlying life processes which affect disease and human well-being, including such areas as cellular and molecular bases of diseases, genetics, [and] immunology." Only in a footnote does it add that a "full list" of activities "includes clinical trials". Thus, despite acknowledging that biomedical research may encompass a broad range of activities more or less corresponding to medical research, the OECD reflects the dominant view that biomedical research is defined by its use of knowledge of biological processes generated in the laboratory to advance human health.

2 The collective memory of biomedicine

This style of biomedical research is embodied in the collective memory of biomedicine's public successes.[18] The rise of biomedicine, as well as its current legitimacy, owes much to the power of these stories and memories of success. These narratives serve as models for imitation and as inspiration for research policy initiatives. Historians have now critically examined some of the most influential of these stories, in particular that of the discovery of penicillin by Ian Fleming in 1928 and that of the genetic basis of sickle cell anemia by Linus Pauling in 1949. A comparison of popular and scholarly narratives shows important differences between the collective memory of biomedicine and historical events. This suggests that the success of biomedicine has a more complex explanation than the straightforward application of laboratory methods.

2.1 Penicillin discovered in the laboratory?

The standard story of the discovery of penicillin is well known. In 1928, Alexander Fleming discovered the antibacterial effect of the penicillium mold while performing bacteriological experiments in his laboratory in London. His discovery was applied to the clinic through the manufacture of penicillin, a powerful antibiotic drug which has saved countless lives. The image of Fleming singlehandedly discovering a new drug in the laboratory has served as an influential narrative to reinforce the status of the laboratory in medical research. Yet recent historical work has demonstrated that this image is largely mythical. The production of penicillin in sufficient amounts and with the required purity for therapeutic use has required intense research and development carried out through collaboration among public research in-

18 Strasser 2002.

stitutions and private industry.[19] Once the substance became available, it was unclear precisely what infectious diseases it might cure and how. Extensive clinical research transformed an industrial substance into a powerful drug. The making of the drug penicillin depended as much on innovations in industry (how to manufacture it) and in the clinic (how to use the substance) as in the laboratory (penicillin has an effect *in vitro*).[20]

2.2 Sickle cell anemia, a model for all diseases?

The story of sickle cell anemia is even more relevant for contemporary biomedical research. The physical chemist Linus Pauling, working at the California Institute of Technology, used the latest experimental methods of his day to discover that hemoglobin (an oxygen-carrying molecule in blood) from patients suffering from sickle cell anemia differed from hemoglobin from those who did not have the disease.[21] This result, published in *Science* in 1949 with the title "Sickle cell anemia, a molecular disease," became an exemplar for biomedical research. Pauling's laboratory-based approach has been used as a model for the organization of biomedical research and as an emblem of the laboratory's power in solving medical problems.[22] The paper itself has been cited over a thousand times in the scientific literature and widely read by generations of students in biology and medicine. In fact, the editor in chief of the *Lancet* recommended that every medical student read Pauling's 1949 paper as part of a select canon of great medical texts including Hippocrates.[23]

Pauling's work epitomized a biomedical culture that sought the identification of single genes or molecules to explain complex diseases (or resistance to diseases like malaria) and the corresponding search for single molecules which could act as "magic bullets" to cure complex diseases. Numerous laboratory researchers modeled or justified their laboratory-based research strategies by reference to Pauling. For example, on the fiftieth anniversary of Pauling's paper, two researchers at the National Institutes of Health, Alan N. Schechter and Griffin P. Rodgers, argued in an editorial for the *New England Journal of Medicine* that Pauling's "basic research" was at last "reaching the clinic".[24] This success, in the authors' view, vindicated Pauling's (and the authors') approach to biomedical research and their view of translational research: one that begins in the laboratory and ends in the clinic. Yet sixty years after Pauling's breakthrough, the only treatment for sickle cell anemia to have received approval from the Food and Drugs Administration (FDA), hydroxyurea, was developed as a result of clinical and epidemiological research, not laboratory research of the kind carried out by Pauling.[25]

More recent examples, such as the discovery of genes causing cancers, or "oncogenes", illustrate the same point. In this case, the standard story attributes their discovery to laboratory research in molecular genetics, but ignores the crucial role of clinical work. As the historian Peter Keating and the sociologist Alberto Cambrosio put it: "clinical researchers are either described as 'biologists' or simply written out of the picture."[26] To summarize, the existing body of scholarly work in the history of biomedicine does not support the view that laboratory research is the main (or only) source of therapeutics.

19 Hobby 1985.
20 Bud 2007.
21 Strasser 1999.
22 Strasser 2002.
23 Horton 1997.
24 Schechter & Rodgers 1995.
25 Strasser 2002.
26 Keating & Cambrosio 2001.

3 Biomedicine as medical practice

In order to understand the workings of biomedical research, it is essential to contextualize it within the changing purview and goals of contemporary medical practice, especially with regards to the definitions of diseases, therapy, and more generally the medicalization of society. Indeed, biomedical research, unlike biological research, gains its legitimacy from the contribution it claims to solving medical problems. How these problems are defined thus shapes what counts as a legitimate biomedical research question and thus strongly orients what kind of biomedical research is carried out. It is important to highlight that much biological research, even on humans, does not define itself (or resists being categorized) as part of biomedicine and sometimes enters in competition with the latter for funding and recognition.

3.1 The redefinition of diseases as risks

Anthropologists, sociologists, and historians have shown how modern biomedicine has progressively changed its concepts of disease. The ontological (Virchow's pathological structures or Ehrlich's invading germs) and physiological (Bernard's abnormal physiology) concepts of disease have been supplemented by a "risk" notion of disease.[27] Originating in public health, which seeks to promote the health of *populations* in the aggregate, the risk notion of disease has become integrated in a biomedical discourse as a key concept through which *individual* patients understand their health or illness.[28] Cardiovascular disease and cancer, for example, are two diseases which biomedicine has transformed from distinct moments of illness into lifelong risks experienced by healthy individuals linked to tests for biomedical markers (cholesterol, genes, antigens, etc.) rather than observable symptoms.[29]

3.2 The boundary between therapy and enhancement

Biomedicine has also profoundly changed the goals of medicine. Whereas medicine aimed solely at the restoration of health, biomedicine now offers ways to improve an individual's physical and mental performance, an endless "pursuit of perfection".[30] Hormone replacement therapy, for example, started off as therapy for some of the most severe symptoms of menopause (which itself can hardly be characterized as a "disease") only to become a preferred treatment to keep the skin of postmenopausal women supple.[31] A similar story can be told for Viagra.[32] Similarly, Adderall was first a drug to treat attention deficit hyperactivity disorder before becoming a favorite "competition drug" among college students and laboratory researchers under pressure to improve their performance.[33]

Biomedicine has blurred the boundaries between the restoration of health and the enhancement of the individual. The more general point, however, is that by shifting its aim from the elimination of disease to the management of risks, biomedicine has opened the door to a never-ending pursuit of risk reduction. The management of disease risk factors such as hypertension (or elevated cholesterol levels) is a case in point. The lowering of blood pressure for hypertensive patients can clearly be seen as a therapeutic strategy to avoid some of its cardiovascular consequences. However, can biomedicine provide an unambiguous and objective boundary between normal and abnormal blood pressure? Historical studies suggest that the boundary between normal and abnormal is the product of complex negotiations between the pharmaceutical industry, physicians, and public health authorities. In fact, 'normal' blood pressure ranges have become successively narrower over time, placing more and more people in the category of patients (and customers) "at risk" and thus in need of treatment.[34] In November 2013, the American Heart Association and the American College of Cardiology released new

27 Temkin 1977.
28 Rothstein 2003.
29 Aronowitz 1998; Rosenberg 2009.
30 Rothman & Rothman 2003; Elliott 2003.
31 Watkins 2007.
32 Tone & Watkins 2007.
33 Seppa 2006.
34 Greene 2007.

guidelines recommending that even people with a very low risk of heart disease (7.5% over 10 years) take statins to decrease their cholesterol levels. If followed, this recommendation would increase by 70% the number of healthy persons taking statins. A virulent controversy has erupted around these recommendations, questioning their medical validity and the independence of the experts who formulated them.[35] This illustrates, once again, that health and therapeutic standards are unlikely to be settled by biomedical research alone.

3.3 The biomedicalization of society

The most important point in understanding current biomedicine as a medical practice is that since its inception in the mid-twentieth century biomedicine has contributed to the expanding authority of medicine itself. This is the latest episode in what scholars have referred to as the progressive "medicalization" of society since the nineteenth century.[36] The medicalization process has reflected, and at the same time reinforced, the power of the medical profession in society. The "medicalization of society" refers to the process through which medicine has claimed jurisdiction over physical, mental, behavioral and other conditions by means of, for example, the creation of new disease categories such as "hyperactive disorder" or "premenstrual syndrome".[37] Comparatively few examples of "de-medicalization" exist. The prominent exception which proves the rule was the removal of homosexuality from the Diagnostic and Statistical Manual of Mental Disorders (DSM) II in 1973.[38]

The concept of medicalization has recently been extended by scholars to the concept of "*bio*medicalization", a specific kind of medical transformation.[39] It emphasizes a type of technological and scientific intervention (based less on the "clinical gaze" than the "molecular gaze") as well as the creation of new individual and collective identities ("biosocialities") grounded upon shared biomedical traits (possessing a disease gene).[40] The single most important feature of biomedicalization is the increasing power attributed to genes. From cancer to political leaning and sex drive to criminality, genes have been invoked in explaining a growing number of traits.[41] Explanations of the origins of diseases are crucial because they suggest ways to diagnose and treat diseases and sideline others. Critics charge that genes have been granted an exclusive status in these explanations, to the detriment of explanations including social, cultural, environmental, or behavioral factors.[42] In the case of obesity, for example, critics of biomedicalization have argued that genetic explanations have distracted from the fact that most cases of obesity can also be explained by social, environmental, and behavioral factors which, unlike genes, could be addressed by vigorous public health interventions or changes in agricultural policy.[43]

These arguments suggest that the balance between opportunities for diagnosis and for therapy differ among the various explanations offered for diseases. Definitions of diseases based on clinical signs make diagnosis particularly straightforward but do not directly indicate a route for therapy. Conversely, definitions of infectious diseases based on the nature of the infectious agent, make diagnosis more difficult but directly suggest possible treatments (antibiotics or vaccination). Presently, genetic explanations offer tremendous promises in terms of diagnosis (especially with the decreasing cost of genomics), but less immediate routes towards therapy. Today however, the identification of the complex genetic basis of diseases is helping identify the molecular pathways involved in pathogenesis and thus many potential targets for therapy.

35 Editorial Board 2013; Abramson et al. 2013.
36 Conrad 2007.
37 Knaapen & Weisz 2008; Tone & Watkins 2007.
38 Terry 1999.
39 Clarke et al. 2003; Clarke & Shim 2011; Burri & Dumit 2007.
40 Rabinow 1996; Rose 2006.
41 Nelkin & Lindee 2004.
42 Krimsky & Gruber 2013.
43 Rosenberg 2007, chapter 8.

Part Two

The key issues defining biomedical research

Scholars in the humanities and social sciences have examined the current activity of biomedicine from a number of disciplinary perspectives. In general, their work has almost exclusively focused on biomedicine as a particular form of *medical practice* and its implications for patients, caregivers, and citizens at large. Only a few scholars (such as Jean-Paul Gaudillière, Ilana Löwy, Angela Creager, Alberto Cambrosio and Peter Keating) have chosen to examine biomedicine as a *scientific practice* aiming at producing new knowledge, the focus of the present report. Existing work makes it possible to outline some of the epistemological assumptions of biomedical research and identify the role of its main actors.

4 The epistemological basis of biomedical research

Biomedical research rests on a series of epistemological assumptions which inform the questions it raises and the answers it counts as legitimate. Three assumptions are central to the practice of current biomedicine, as we have defined it above: universalism, reductionism, and modelization. Yet at the beginning of the twenty-first century, these assumptions are increasingly being challenged by developments emerging from biomedical research itself.

4.1 Universalism

From the earliest days of medicine, physicians have sought to understand instances of individual illness as the expression of a more general disease. The rise of bacteriology in the nineteenth century has furthered this trend by defining diseases, such as tuberculosis, as universal categories, recognizable by the presence of a specific infectious agent, which could produce various symptoms in individual patients. The rise of biomedicine has accelerated the tendency to search for universal mechanisms underlying disease. To a large extent, biomedical research is based on inquiry into the biological mechanisms of disease which, like the laws of nature, are believed to possess universal validity. As the molecular biologist François Jacob has put it, nature has a structure that possesses "obvious diversity and hidden unity".[44] Indeed, the professional development of medicine has rested, in large part, on its claim to universal scientific knowledge.[45]
It is against this backdrop that the recent discourse about "personalized medicine", the tailoring of drugs to the individual genetic makeup of patients, should be understood.[46] In 2005, the Food and Drug Administration (FDA) approved BiDil, the first drug targeted at a specific ethnic group (African-Americans), causing widespread debate about the goals of biomedicine. Yet after a closer look, this event seems to be less

44 Jacob 1998, p. 109.
45 Starr 1982, pp. 4, 121–123, 134–135.
46 Roberts et al. 2012.

an indication of a trend towards "personalized medicine" than a reflection of marketing concerns aimed at an American audience.[47] More significant are current attempts to tailor drugs and treatments to individual genetic backgrounds[48] or the rise of direct-to-consumer personalized genomic services, both of which mark a shift away from a centuries-long trend towards universalism.

4.2 Reductionism

Like most experimental research in the life sciences since the nineteenth century, the search for biological mechanisms of diseases has followed a reductionist agenda, in opposition to more holistic attempts to understand life.[49] As the philosopher of biology Michael Ruse has made clear, advocates of reductionism can make at least three distinct claims:

a) an ontological claim: the whole *is* nothing more than the sum of the parts;
b) an epistemological claim: the whole is best *explained* by referring to the parts;
c) a methodological claim: the whole is best *studied* by exploring the parts.[50]

Specifically, this has meant a focus on molecules, including genes, and their role in health and disease. The rise of molecular biology in the mid-twentieth century perfectly illustrates this approach, but should be considered an episode in a longer history of biological reductionism.[51]

In its application to medicine, the reductionist view of the body has faced considerable difficulties as well as challenges from advocates of a "holistic" approach to health. These new "holistic" approaches, it should be stressed, are not identical with older forms of "holism", such as those of the nineteenth-century Romantics, which searched beyond matter for explanation of biological processes. Rather, contemporary holists stress the importance of systems (as in "systems biology") and relations between bodies and their environments rather than singling out entities on the smallest possible scale.[52]

4.3 Modelization

The power of experimentation, in biology and the other sciences, results from the fact that variables of the system under scrutiny can be carefully controlled. For this reason, most experiments are conducted, not in nature, but in laboratories, where these variables can be individually adjusted in order to allow experimental replication. For the same reason, experiments are conducted on human-made systems, which are as uniform and replicable as possible. Although they are the product of human artifice, these systems are believed to represent the natural phenomena taking place outside the laboratory. They are considered "model systems" or "model organisms" which are capable of standing in or substituting for more complex phenomena in nature.[53] In the biomedical sciences, the experimental study of biological processes has predominantly taken place in a few model organisms, especially mice, flies, worms, yeasts, bacteria, and viruses.[54] These organisms were often chosen for practical reasons (small size, rate of reproduction) and taken as exemplars to study particular phenomena (cancer, heredity, development).[55] As the molecular biologists Jacques Monod and François Jacob famously put it, "[What is] true of *E. coli* must also be true of Elephants."[56]

This assumption gave tremendous power to the biomedical research enterprise. With the assumptions of universalism and reductionism, model organisms became one of the most powerful research tools for biomedicine.[57] Since scientists could investigate simple organisms and draw conclusions about humans (or elephants), *all* biological research became potentially relevant to medicine. Of particular significance for biomedicine was the role of mice as a substi-

47 Kahn 2013.
48 Kohli–Laven et al. 2011.
49 Allen 1975; Coleman 1978.
50 Sarkar 1998.
51 On the history of molecular biology, see Morange 2000; on the molecularization of the life sciences, see de Chadarevian & Kamminga 1998.
52 On holism, see Rosenberg 2007, chapter 8; on the limits of reductionism in pathology, see Keating & Cambrosio 2004.
53 On model systems, see Rheinberger 1997.
54 Endersby 2007.
55 Ankeny & Leonelli 2011.
56 Monod & Jacob 1961.
57 On the place of models in science more generally, see Creager, Lunbeck and Wise 2007.

tute for humans. In the 1930s, mice became the main model for the study of cancer, thanks to a vast program of genetic standardization and industrial breeding at the Jackson Laboratory in Bar Harbor, USA.[58] This approach has oriented biomedical explanations in specific directions. The Jackson Laboratory for example, chose to pursue the experimental study of cancer through the use of highly inbred mice specifically selected to produce particular kinds of cancers. The results of these investigations, unsurprisingly, reinforced the view that the genetic material is a principal cause of human cancer. Had non-inbred mice been employed, chemical or viral causes might have appeared to be more probable.

58 Rader 2004.

5 The actors of biomedical research

A third essential component in the characterization of biomedical research, after the practices and values outlined above, is the different actors that directly or indirectly contribute to the production of knowledge. Universities, philanthropies, hospitals, industries, start-ups, and patient organizations have been some of the main (institutional) contributors to the development of biomedicine and those who defined the place and meaning of biomedical research in the larger research landscape.

5.1 Universities, philanthropies, and the biomedical complex

At the beginning of the twentieth century, biomedicine's emphasis on laboratory research, especially biological research, accorded to universities a central position in its development. However, before the middle of the century the extent of academic research was limited by the fact that universities received modest state support for their activities. Nation states only became major patrons of scientific research after 1945. There was also little support from industry. During the 1930s several pharmaceutical companies did sponsor extensive laboratory work as part of their research and development programs, but these efforts focused on chemical approaches to drug development based on the synthesis of chemical derivatives and their testing, not biological research.[59]

These conditions amplified the influence of the one set of organizations that did actively seek to sponsor biomedical research in the early twentieth century: private foundations such as the Carnegie Institute of Washington or the Rockefeller Foundation.[60] Private foundations were able to exert considerable influence over the direction of biomedical research as a field,

59 Lesch 2007.
60 Kohler 1991.

although the extent to which their influence altered the research agendas of individual scientists is still a matter of debate among historians. The Rockefeller Foundation, for example, supported a number of research projects, such as Pauling's study of sickle-cell anemia, aiming at a better understanding of the biological basis of health, disease, and behavior, but declined to support more "holistic" approaches.[61] Overall, it strongly supported the rise of molecular biology, which played a leading role in shaping biomedicine as a laboratory science, at a crucial time when its approaches fell outside traditional academic disciplines and had difficulty finding institutional support. For example, just after the Second World War, the Rockefeller Foundation played a key role in supporting the reconstruction of European science, strengthening its prewar involvement, by encouraging the mobility of researchers, the organization of international conferences, and crucially, the purchase of expensive scientific instruments for biomedical research.[62] These instruments, such as electron microscopes, ultracentrifuges or electrophoresis apparatus, made it possible for European research to adopt the specific research practices that were central to biomedicine at a specific time in history when American research practices were increasingly becoming the international standard. In the prewar period, European researchers were often leaders in their fields of biomedical research (think of the Tadeus Reichstein synthesis of vitamin C and Leopold Ružička synthesis of sex hormones in Zurich), but after the war, the center of gravity of scientific excellence temporarily moved across the Atlantic.

With the rise of the nation states as the major patrons of scientific research in the 1950s, the scale of academic research vastly expanded. Although not as expensive as "big science" projects in physics or astronomy, biomedical research was much more expensive than naturalist biology and thus critically indebted to state funding. Government patronage for this expansion was available because health research, like national security, had emerged as a key priority for most nation states. Universities carrying out biomedical research received a significant share of state funding. The fact that the National Institutes of Health always possessed a budget vastly larger than the National Science Foundation reflects this set of priorities.[63] Similarly, at the creation of the Swiss National Science Foundation in 1952, biology and medicine were singled out to be part of an independent division, on par with the two others, devoted to all the humanities and social science or all the natural sciences, mathematics and engineering.[64] In the case of Switzerland, the rise of science policy during the Cold War brought the federal government to play an increasingly active role in defining research priorities and funding them through targeted programs.[65] Biomedical research in universities was one of the main beneficiaries of these targeted initiatives, such as Nixon's 1971 "War on Cancer". The tendency only accelerated after the end of the Cold War, and the attribution in 2013 of an EU "Flagship" grant to the EPFL's Human Brain Project reflects the emphasis on targeted biomedical research as well. The extent to which states should and can direct the orientations of scientific research and the impact of state direction on the production of knowledge is still a hotly debated topic among scholars.

In several cases, the rise of biomedicine was supported by creation of new state institutions, operating at a national level, such as the Institut National de la Santé et de la Recherche Médicale (INSERM) in France, the National Cancer Institute (NCI) in the United States or at the state ("canton") level in Switzerland, such as the Basel Institute of Immunology (in 1969 by Hoffmann-la-Roche) or the Friedrich Miescher Institute (in 1970 by Ciba and Geigy). The NCI was founded in 1937 as a small government laboratory and soon integrated into the National Institutes of Health (NIH). In the 1940s, taking inspiration from the successful search for antibiotics against infectious diseases, the American Cancer Society and the Lasker Foundation identified the screening of compounds for chemotherapy as the most promising approach to producing a cure for cancer. This attempt to find a "magic bullet" required a vast number of laboratory animals, chemical compounds, and patients. Because such an effort was beyond the means of any existing research institution in 1955, the American Cancer Society lobbied the United

61 For the view that foundations played a major role, see Kay 1993; for a view that they did not, see Abir-Am 2002.
62 Gemelli, Picard and Schneider 1999; Picard 1999.
63 Wright 1994, chapter 1; Appel 2000.
64 Fleury & Joye 2002.
65 Joye-Cagnard 2010; Benninghoff and Leresche 2003.

States Congress to create the Cancer Chemotherapy National Service Center within the NCI. This program conducted large-scale screening operations and coordinated the efforts of pharmaceutical companies, universities, and private hospitals.[66] The new program had a dramatic impact on numerous biomedical practices: it helped promote the acceptance of mouse models of human diseases, fostered the coordination of laboratory and clinical work, and assisted the development of the randomized control trial for the assessment of new drugs.[67] The NCI became a major player in biomedical research and expanded its activities in the 1960s from screening into more fundamental inquiries regarding the nature of carcinogenesis. For example, the NCI sought to find and identify human cancer viruses and develop a cancer vaccine via an ambitious NASA-style program. While this effort fell short of its aims, it sponsored research in molecular genetics and virology which shaped and accelerated the development of those fields, especially the discovery of oncogenes and anti-oncogenes (or tumor suppressor genes) such as p53, *Science*'s 1993 "molecule of the year".[68] As the example of the NCI shows, the growth of the NIH reflected the degree of political mobilization behind particular diseases—creating an awkward fit between promoting a broad program of research in the life sciences and providing evidence that research money it allocates concretely promotes the cure of diseases.[69]

5.2 Hospitals and the rise of randomized clinical trials

Although most histories of biomedicine focus on the successes of laboratory research, clinical research has been no less important for the development of biomedical knowledge. The single most important element in making hospitals part of the biomedical research enterprise was the development of randomized clinical trials (RCT).[70] Modeled explicitly after the epistemic standards of the experimental sciences, the RCT developed in the 1940s as a set of procedures to "objectively" evaluate the efficacy of drugs. Before the RCT, questions of therapeutic efficacy were mainly adjudicated through the experience and expertise of individual or small groups of physicians, through their observation of individual patients. The efficacy of a particular treatment rested thus on the personal credibility of the physician rather than on a standardized method, like the one the RCT came to represent.

After the Second World War nation states assumed greater responsibility for regulating the safety and efficacy of drugs. This new responsibility accelerated the adoption of the RCT as a standard procedure. For regulatory agencies, such as the United States Food and Drug Administration, the RCT promised an objective and scientific means of testing the safety and efficacy of drugs and a non-arbitrary basis for their decisions.[71] It can be tempting to see the RCT solely as a test applying scientific standards to determine the efficacy of a drug developed in a laboratory for human subjects. As recent work in the history of biomedicine makes clear, this is a gross oversimplification. RCTs have served as a place where more complex knowledge about disease is produced. As historian of medicine Ilana Löwy has shown, clinical trials in hospitals are, no less than experiments in laboratories, practices producing knowledge about the workings of diseases as well as their possible treatments.[72] Clinical trials are the place where the *relation* between therapeutic agents and diseases are defined, which means that new definitions of diseases and target populations are a possible outcome of clinical trials, not only verdicts about the efficacy of new drugs on existing diseases.[73]

For the RCT to function as a potentially objective basis for evaluating drug efficiency, it is crucial that all the results, positive and negative, be recorded. Yet, as sociologist Sheldon Krimsky has shown, the majority of RCTs are sponsored by industry which rarely publicizes negative results.[74] As a result, many states have established clinical trial registries, such as the National Library of Medicine's Clinicaltrials.gov in the United States, where trials are registered before their outcomes are known, making it possible to track the results in a less biased way.

66 Goodman & Walsh 2001.
67 Gaudillière 1994; Löwy 1996; Keating & Cambrosio 2012.
68 Gaudillière 1998.
69 Thomas 1977.
70 Marks 1997; Keating & Cambrosio 2012.
71 Carpenter 2010.
72 Löwy 1996.
73 Kahn 2013.
74 Krimsky 2003.

The centralization of clinical trial registration has been all the more necessary now that trials are becoming an increasingly globalized enterprise.[75] As anthropologist Adriana Petryna has pointed out, "clinical research is now a worldwide data-making enterprise" with industries carrying out a growing number of trials in developing countries, out of the reach of national regulatory regimes for RCT.

5.3 The pharmaceutical industry

The pharmaceutical industry has played a major role in the development of biomedical knowledge; however, that role profoundly changed in the twentieth century. As the economic historian Alfred D. Chandler Jr. has argued, the pharmaceutical industry sector was remarkably stable for most of the twentieth century: the main pharmaceutical companies operating at the end of the century were the same as those at the beginning of the century.[76] He explains this stability by the unusually high knowledge barrier, protected by patents, for entry into the field of pharmaceutical research. Yet behind this apparent stability, deep changes have taken place in the research strategies of the pharmaceutical industry. In Switzerland, Germany, France and the United Kingdom, the pharmaceutical industry grew out of the nineteenth-century chemical, and especially dye, industries.[77] It based its search for new drugs on the chemical synthesis of a large number of molecules and their subsequent screening for biological effects.[78] This model of innovation, based on the medical researcher Paul Ehrlich's vision of a "chemotherapy" through "magic bullets" resulted in the development of Salvarsan by IG Farben in 1910, the first "chemical" drug for the treatment of syphilis and, more significantly, of Prontosil by Bayer AG in 1932 (the "first miracle drug"), and other sulfa drugs for the treatment of bacterial infections.[79] Screening of synthetic and purified chemical compounds has remained a central strategy for drug discovery to the present day. In addition, however, a precise knowledge of the chemical and molecular structures of biological targets has made it possible to design (or select) molecules that might have a therapeutic effect. This "rational drug design" approach rests on the reductionist assumption that disease can be reduced to simple molecular pathways and that therapeutics should aim at single targets. Although this approach has had some success, such as the development of Gleevec, it is debated to what extent this approach can be generalized or how cost-effective it might be.[80]

Critical to understanding the rise of biomedicine is the shift from a strategy exclusively based on synthesis and screening to one based on seeking an understanding of the basic biological mechanism of diseases. In the case of the Swiss pharmaceutical firm F. Hoffmann-la-Roche, this shift in strategy began in the 1960s and involved a major institutional transformation since the company did not possess the research expertise in (molecular) biology required by such a reorientation.[81] Biologists, unlike chemists, were often reluctant to work for the pharmaceutical industry, making it all the more difficult to recruit them.[82] The industry resorted to the creation of new forms of collaboration with biologists in academia, for example by the creation of private research institutions modeled after academic departments, such as the previously mentioned Basel Institute of Immunology (by Hoffmann-la-Roche) or the Friedrich Miescher Institute (by Ciba and Geigy), and collaborating with academic departments such as the Biozentrum at the University of Basel, in order to secure the required expertise.[83]

The close relationship between the pharmaceutical industry and academic research has been reinforced by the nature of the biological substances being investigated. In the case of the anticancer drug interferon, academic research on its biological effects required significant amounts of the molecule that only industry could provide. Conversely, industry was only interested in synthesizing significant amounts of the molecule if it showed promise as a cancer treatment.[84] The

75 Petryna 2009.
76 Chandler 2005.
77 Travis 1993.
78 Sneader 2005.
79 Hüntelmann 2011; Lesch 2007.
80 Folkers 2011; Lesch 2008.
81 Bürgi & Strasser 2010.
82 Bürgi 2011.
83 Bürgi 2011. On earlier collaborations with academic medical researchers, see Swann 1988 and Rasmussen 2004.
84 Pieters 2005, chapters 3–4.

study of interferon thus required negotiation between biologists and industry rather than a simple transfer of knowledge.

Recently, criticism concerning the pharmaceutical industry's drug pricing structures and the lack of biomedical research on widespread but less-profitable diseases has resulted in the creation of the first non-profit drug development organizations.[85] These organizations attempt to combat the "90/10 research divide", i.e. the fact that only 10% of drug research is focused on 90% of the "global disease burden".[86] Founded in 2000 with the support of the Bill and Melinda Gates Foundation, the Institute for OneWorld Health, for example, has developed a drug against visceral leishmaniasis, a deadly disease which kills around 60,000 people annually. It has also focused on other neglected diseases, such as cholera, malaria, and helminthiasis, in collaboration with public and private research institutions including the Swiss Tropical and Public Health Institute, Novartis, and Roche.[87]

5.4 The state and regulation

Nation states have profoundly influenced the development of biomedicine through the regulation of pharmaceuticals, the creation of intellectual property regimes for biological discoveries, and the sponsorship of health insurance. These three domains of state regulations will be examined consecutively. In the United States, the Food and Drug Administration (FDA) held limited power to regulate the drug market until 1938. Following the Elixir sulfanilamide scandal (a tainted sulfa drug produced in 1937), the US Congress passed a legislation requiring that every new drug receive an authorization from the FDA which would be delivered only if the manufacture could prove that the drug was toxicologically safe. However, new drugs could still be tested by physicians without authorization and could be authorized without having been clinically tested. The thalidomide scandal in 1961 (a sedative with teratogenic effects on fetuses) prompted Congress to pass the 1962 Kefauver-Harris act, which defined the key principles of drug regulation in the United States and in Europe as they function today.[88] Extensive laboratory testing was required *before* a drug could undergo clinical testing and the clinical demonstration of drug safety *and* efficacy were required before a drug could be brought to the market. Intended to promote drug safety, the requirements of these measures also favored large established pharmaceutical companies. Only they had the capacity to perform basic biological research (either in house or in collaboration with academia) and to establish the relationships with medical schools and hospitals necessary for carrying out clinical trials.

In Europe, drug regulation has proceeded along similar lines (in Switzerland, Swissmedic has held responsibility for drug authorization since 2002) although with significant differences.[89] In the United States, the process of drug authorization is largely public, leading to the involvement of many advocacy groups, whereas in Europe, it is essentially confined to professional experts from government and industry.[90] In the United States, the more visible regulatory process leads to wide public debates which have an impact on the public's understanding of biomedical research.

The pharmaceutical industry has lobbied to relax some of the stringent regulations set up by the FDA. In the United States, it has successfully obtained the legalization of direct-to-consumer advertisement, resulting in dramatically increased drug consumption and making individuals ever more dependent on the products of biomedical research. Critics of this shift, such as the physician Marcia Angell, former Editor-in-Chief of *The New England Journal of Medicine*, argue that the rapidly rising cost of drugs is not mainly due to research expenses, including those necessary to satisfy drug safety regulation, but rather to the cost of marketing campaigns and the profit margins sought by the industry.[91]

85 Hale et al. 2005.
86 Petryna 2009, p. 194.
87 Swiss TPH 2011.
88 Daemmrich 2004.
89 Gaudillière & Hess 2012.
90 Daemmrich 2004.
91 Angell 2005.

Industry has also succeeded in progressively shifting the burden of proof for drug safety from the pre- to the post-marketing phase. Without extensive premarket testing, drugs can be made available more readily, their safety being ensured by post-marketing surveillance. However, for the majority of drugs released following these regulations, post-marketing studies have not been reported to the FDA.[92] Whether or not this has compromised drug safety and contributed to the increase in drug withdrawals, such as Rofecoxib (Vioxx), is still heavily debated.

The second area where the regulations of nation states have had a major impact on the development of biomedicine was in defining the intellectual property regimes concerning drugs and biological materials. In Europe, and especially in France, drugs were originally excluded from the protections of intellectual property law because of their importance for human health.[93] However, after the Second World War, the United Kingdom (1949), France (1959), and Germany (1965), for example, passed legislation authorizing the patenting of therapeutic substances.[94] According to historian of science Jean-Paul Gaudillière, these acts should be understood as part of the modernization efforts of postwar states to foster scientific research in service of economic growth.[95]

The extension of patent protection played a particularly significant role in stimulating the rise of the biotechnology industry (see next section) in which new therapeutics and research methods were based, not on chemical synthesis or extraction, but on the production of substances through genetically modified organisms. In 1980, the Supreme Court of the United States ruled in *Diamond vs. Chakrabarty*, in a 5–4 decision, that "live, human-made micro-organism is patentable subject matter."[96] This decision paved the way for the patenting of transgenic animals (OncoMouse™), plants, tissues, cells, and molecules, including genes, such as the BRCA (breast cancer) genes.[97] In addition to their moral dimension, the implication of human gene patents on the costs of health care has made them a particularly controversial issue. A series of legal challenges against Myriad Genetics, who held the patents on the BRCA genes and sold exclusive genetic tests for breast cancer, led the Supreme Court of the United States to the unanimous decision, in June 2013, barring the patenting of human genes.[98]

One more aspect of intellectual property regulation has had an important impact on the development of biomedicine: the passage in the United States of the Bayh-Dole Act in 1980. The Act authorized universities and other non-profit organizations to seek patents on the results of federally funded research. As a result, private and public universities created or reinforced their technology transfer offices and encouraged their researchers to develop patentable materials. In Europe, the creation of technology transfer offices has been much slower, and in Switzerland, the majority was created after 1990.[99] Bristol-Myers Squibb's bestselling anti-HIV drug Zerit, is a good example of how intellectual property regulation can benefit research universities. Zerit is based on a molecule identified by the Yale chemist William Prusoff and patented by Yale University. Licensing of the patent earned Yale University almost $40 million per year.[100] The pressure to produce economically valuable research has been often criticized for its negative side effects. Scholars have pointed out that only a few patents, such as the Stavudine patent, result in significant revenues for universities which can be invested in further research. Most patents remain unexploited, and for many universities, the patenting process costs more than any revenues it generates. Moreover, it has been argued that by increasingly focusing on research topics which could be commercially lucrative, academic research might leave aside more basic questions which nobody else would investigate.[101]

Finally, the regulation of health insurance, especially in countries with universal health care, with respect to the reimbursement of drugs and treatments has an important impact on the therapeutic market and thus on biomedical research. The impact of public policies encouraging the prescription of generics, for example, on biomedical research carried out by the pharmaceutical industry is hotly debated. While one might expect the promotion of generics to have a chilling effect

92 Shuren 2008.
93 Cassier 2004.
94 Gaudillière 2008.
95 Gaudillière 2002.
96 Kevles 1998.
97 Kevles 2002.
98 Liptak 2013.
99 Wadman 2008.
100 Demenet 2002.
101 Geiger 2004.

on industry research into related drugs, the physician and historian of medicine Jeremy Greene has argued that the concept of "biological equivalence" between a brand name and a generic drug was sufficiently flexible to allow the pharmaceutical industry to maintain a firm hold on the market through branded drugs even though cheaper generics were available.[102]

5.5 Biotech companies

The rise of the biotech industry is perhaps the most visible institutional transformation associated with the development of biomedicine.[103] In the early 1970s, a number of new companies were created with venture capital to pursue biomedical research with the new tools of genetic engineering, such as Biogen (founded in Geneva in 1976) and Genentech (founded in San Francisco in 1978).[104] Known as recombinant DNA technology, these tools, developed mainly between 1972 and 1974, made it possible to join DNA from different organisms. This allowed researchers to use bacteria to produce unlimited amounts of genes and gene products, for example human insulin, in large fermenters. Although biological processes have been used for production purposes for centuries (the production of beer, wine, and cheese for example),[105] these new biotechnologies made it possible, once the corresponding gene was isolated, to produce almost any protein in unlimited quantities with a high degree of purity.

The new biotechnology industry focused on the isolation of specific genes and the development of new techniques for their manipulation. Genentech, for example, founded by the Stanford biologist Herbert W. Boyer and the venture capitalist Robert A. Swanson, focused on developing techniques to produce a human growth hormone, somatostatin, and later insulin, in bacteria.[106] These efforts were directed by a new breed of scientists, which have become common since, the scientist-entrepreneur, adept at navigating between the academic and corporate worlds and fostering the convergence of these two previously antagonistic cultures.[107] The typical commercial products of the biotech industry are not drugs, but patents on specific methods, which are then licensed or sold to larger pharmaceutical companies. The fragile economic structure of start-up companies, requiring constant infusions of fresh money, constrained their research agendas. It was essential to produce results quickly and maintain a sense of optimism that major breakthroughs were imminent. The high costs of clinical trials and drug development have often caused biotech companies to seek alliances with larger pharmaceutical companies or to focus on the development of research methods, rather than drugs. The development and patenting of the polymerase chain reaction (PCR), a technique to amplify large amounts of DNA, by the small biotech firm Cetus is a case in point.[108] After start-up companies grew to a certain size, they sometimes issued public offerings and their stock traded on Wall Street. Genentech, for example, went public in 1980 and its share prices more than doubled on the first day, reflecting the heightened promise of the new industry.[109] In 2009, Genentech was bought by the pharmaceutical giant, F. Hoffmann-la Roche, completing a common life cycle for a biotech start-up company.

The most striking novelty of the biotech industry is how it has provided a new space between industry and academia where biomedical innovation could take place. The close links between the biotech industry and academic researchers has been essential to their success, providing crucial scientific expertise and the institutional credibility needed to convince investors to provide funding. The boom of the biotech industry in specific geographical clusters, such as the San Francisco Bay Area or Boston's Route 128 corridor, associated with a high concentration of leading universities (Stanford, Berkeley, UCSF and Harvard, MIT respectively) has led some to argue that, in the case of the computer and biotechnology industries, academic excellence *per se* was an engine of economic growth. But a detailed study of successful biotechnology clusters has shown that they relied as much on research excellence as on pre-existing commercial ac-

102 Greene 2011; Carpenter & Tobbell 2011.
103 Kenney 1986.
104 Vettel 2006.
105 Bud 1993.
106 Kleinman 2003.
107 Vallas & Kleinman 2007.
108 Rabinow 1996.
109 Krimsky 1991, pp. 21–42.

tivity in the field. This activity provided support to the emerging biotech companies which generally operated at a financial loss due to their investment in research and lack of marketable products.[110] Similarly, in her study of failed attempts to build such clusters in Atlanta or Philadelphia, the urban planner Margaret Pugh O'Mara shows that a number of extrinsic factors, such as the availability of land, public support, and the social environment, are just as important as the existence of scientific expertise.[111]

It comes as no surprise then that the patterns of university-biotechnology-industry relationships have evolved differently in the United States and in Europe. In short, these relationships developed much later in Europe than in the United States, were on a small scale, and displayed much less integration of basic research with clinical development.[112] The specialization of European research institutions (such as the Max Planck Institutes), the cultural isolation of universities from corporate values, the access to venture capital, or the lack of personal incentives to merge academic and corporate work might also explain the relative weakness of the European biotechnology sector.

5.6 Patient organizations

During most of the twentieth century, patients were mainly passive *objects* of biomedical research, but today they have become active *subjects* in the production of biomedical knowledge. Patient organizations have played an especially important role in this regard, influencing science policy and research agendas and raising money to support biomedical research on specific diseases, following the model of public philanthropy. Most famously, the March of Dimes Foundation, founded in 1938, raised money from the American public to support research aiming at the development of a polio vaccine, eventually leading to the Salk vaccine in 1955.[113] In the 1980s and 1990s, the fundraising telethons of the Association Française Contre les Myopathies (AFM) played a significant role in the study of the genetic basis of muscular dystrophy, leading to the identification of the first gene related to Duchenne muscular dystrophy.[114] The most profound shift in the role of patient organizations occurred with the beginning of the AIDS epidemic. As the sociologist Steven Epstein has shown, patient organizations such as Act-Up, not only provided financial support for scientific research on AIDS, but also claimed a form of "lay expertise" that contributed to the production of scientific knowledge about the disease.[115] Similarly, as the sociologists Vololona Rabeharisoa and Michel Callon have shown, patients with muscular dystrophy and their families, organized through the AFM, acquired academic expertise or worked with academics to produce scientific knowledge about their disease.[116] This model for the production of biomedical knowledge could become increasingly important as companies selling direct-to-consumer genetic tests, such as 23andMe, encourage their clients to provide biomedical information in order to aid the identification of the genetic basis for specific conditions.[117] The growing importance of patient organizations, as a source of knowledge and legitimacy, has also made them a prime focus of the pharmaceutical industry's research and marketing strategies.

110 Cortright and Mayer 2002.
111 O'Mara 2005.
112 Owen-Smith et al. 2002.
113 Oshinsky 2005.
114 Rabinow 1999.
115 Epstein 1996.
116 Rabeharisoa & Callon 2002.
117 Prainsack & Wolinsky 2010; Yurkiewicz 2010.

Part Three

Possible futures

The scholarly work in the humanities and social sciences about the recent past of biomedicine helps us bring current changes into perspective and outline possible futures of biomedicine. The study of the past also highlights topics, actors, and issues that have been essential in shaping current biomedicine and that should thus be taken into account in framing future policies.

6 The futures of biomedical research

An increasing number of commentators are pointing to the fact that biomedical research is at a crossroad for economic and scientific reasons. First, it is often claimed that the pharmaceutical industry is facing an "innovation crisis", a failure to bring new drugs to the market. However, as a recent analysis in the *British Medical Journal* pointed out, the problem is not the failure to bring new drugs to the market (that number has been fairly constant for decades), but the failure to produce new drugs with significant therapeutic benefits rather than "me too" drugs, simple substitutes for existing therapeutics, which account for as much as 85%–90% of all new drugs.[118] Furthermore, the growing cost of health care among all industrialized countries has raised concerns about drug pricing.[119] The pharmaceutical industry has justified the high price of drugs by the fact that each drug requires the investment of between $800 million and $2 billion in biomedical research.[120] However, independent analysts point to the fact that investment in R&D was closer to $100 million, with ten to twenty times as much spent on drug marketing and promotion.[121] Whatever the exact reasons for the exploding costs of therapeutics, the ability of biomedical research, as it is currently organized, to provide cost-effective health benefits is being increasingly challenged.

Second, the core intellectual framework for biomedical research has come under question. Throughout the twentieth century, the idea that unique genes determined physical traits and diseases has driven biomedical research. In mid-century, the rise of molecular biology brought DNA, the molecule genes are made of, to the leading status of "master molecule" of the cell (and the entire organism) and justified the sequencing of the human genome.[122] Yet, a decade after its completion it seems that only a small minority of diseases results from just one or a few altered genes. The famous examples of sickle cell anemia, cystic fibrosis or

118 Light & Lexchin 2012.
119 Brill 2013.
120 Paul et al. 2010.
121 Light & Lexchin 2012.
122 Keller 2000.

breast cancer are the exception rather than the rule. Even in the case of breast cancer, although a mutation in the BRCA1 and BRCA2 genes gives a high probability of developing breast cancer, only 20% of breast cancer patients carry a mutation in these genes.[123] Other associations between single genes and diseases typically only increase overall risks of developing the disease by 1–2%, leaving the rest to be explained differently.[124] For the great majority of diseases, including the most widespread causes of death such as heart disease and cancer, genome-wide association studies (GWAS) have shown that a very large number of genes make a very small contribution to the inheritance of these diseases.[125] Although these results may be important to identify biological pathways involved in pathogenesis,[126] they offer little immediate hope for direct therapeutic of even diagnostic intervention. Consequently, current biomedical research is shifting towards the identification of genome networks, rather than individual genes.[127] The simplistic view of genetic determinism has been complicated by the recognition of the role of epigenetic phenomena, i.e. inheritable changes in gene expression which are not linked to changes in DNA sequence.[128] The importance of epigenetic mechanisms for biomedicine lies in the fact that they are affected by diet, behavior, and the environment, recasting the standard division between nature and nurture.[129] Thus, even the study of the inheritable component of diseases can not solely focus on genome sequences, but must take environmental factors into account.

In short, the causes and mechanisms of diseases seem today far more complex than the proponents of biomedicine have envisioned. One key problem facing biomedicine is how to master this complexity in order to produce knowledge that can yield significant health benefits (in addition to the intrinsic value of gaining new knowledge). To do so, current biomedical researchers are building databases to collect, compare, compute, and classify massive amounts of data.

In recent years, improvements in various technologies, such as DNA sequencing, have led to the production of immense amounts of data, leading several commentators to announce the coming of age of a new "data-driven" science.[130] Instead of using biomedical experimentation to test various hypotheses, the new approach consists in identifying patterns in data to "discover things we neither knew or expected".[131] In 2013, for example, the *Lancet* reported the results of a study of the genome of over 60,000 people, half of which with schizophrenia, bipolar disorder, autism, major depression, or attention deficit hyperactivity disorder, psychiatric diseases which were believed to have little in common. Analyzing this massive amount of data, the researchers found that those with these disorders shared a genetic change affecting a protein involved in neuron signaling and suggested that it should be targeted for treatment.[132] More importantly, perhaps, they suggest, along with other researchers, that the classification of diseases should be based on their genetic basis.[133]

The field of bioinformatics has grown rapidly around the capacity to create databases, which can serve as tools for the production of knowledge. Some researchers have criticized the usefulness of an approach solely based on the analysis of data, rather than the experimental testing of hypothesis, or have questioned the radical novelty of this approach.[134] However, there is a broad consensus that the development of databases and bioinformatics tools is increasingly necessary for the progress of biomedical research. Indeed, they can represent powerful instruments, together with statistical methods, to overcome the complexity of biomedical data and, most importantly, allow the integration of diverse sources of experimental and clinical data.

123 Meindl et al. 2011.
124 Goldstein 2009.
125 Dermitzakis 2012.
126 Hirschhorn 2009.
127 Califano et al. 2012.
128 Kilpinen & Dermitzakis 2012.
129 Keller 2010.
130 Hey et al. 2009.
131 Brown & Botstein 1999.
132 Cross-Disorder Group of the Psychiatric Genomics Consortium 2013.
133 Pollack 2008.
134 Strasser 2008; Strasser 2012, pp. 85–87.

7 Conclusions

The success and failures of past biomedical research as well as its current transformation point to several factors which are crucial for the future development of biomedicine. We will outline three areas: the integration of clinical and laboratory research, the relationships between academic and commercial research, and the access to scientific knowledge.

First, as the history of biomedical research makes clear, the integration of laboratory and clinical research is critical to the successful development of new therapeutics. Many of the unfulfilled promises of biomedicine resulted from a simplistic view of the application of basic biological knowledge to clinical practice. Bridging the gap between the laboratory and the clinic is an extremely complex endeavor and it seems clear that trivializing this effort is not helpful.

Three factors are particularly important to take into consideration when thinking about the best ways to bridge this gap:

1) How are academic biologists and physicians trained?[135]
2) Where are biological and clinical research facilities physically located?[136]
3) How are biological and medical research departments institutionally organized?[137]

Second, public-private partnerships are essential for the development of therapeutics, yet many commentators argue that there is much room for improvement in this relationship. At least three factors are important to take into account:

1) What kind of entrepreneurial training do biologists and physicians receive?
2) How are intellectual property rights regulated?[138]
3) How impartial is the evaluation of therapeutics?[139]

Thirdly, in order to overcome the complexity and variability of biological mechanisms, researchers increasingly rely on large databases and tools to integrate data from different fields. This approach requires new infrastructures for biomedical research and a different evaluation of the value of biomedical research. Efforts towards improving these infrastructures have focused on at least three factors:

1) How are data infrastructures funded?[140]
2) How is biomedical data-driven research evaluated?[141]
3) How is access to databanks regulated?[142]

The futures of biomedical research depend on many more factors, but those mentioned above are all crucial in determining how biomedical research will look tomorrow.

135 Zemlo et al. 2000.
136 Keating & Cambrosio 2003.
137 Wadman 2013.
138 Geiger & Creso 2008.
139 Krimsky 2003; Angell 2005.
140 Strasser 2011.
141 O'Malley et al. 2009.
142 Edwards et al. 2013.

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Abbreviations

AFM	Association Française contre les Myopathies
AG	Aktiengesellschaft
AIDS	Acquired immune deficiency syndrome
BRCA	Breast cancer susceptibility gene
CSSI	Conseil suisse de la science et de l'innovation
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
E. coli	Escherichia coli
EPFL	Ecole polytechnique fédérale de Lausanne
EU	European Union
FDA	Food and Drugs Administration
GWAS	Genome-wide association study
HIV	Human immunodeficiency virus
IG	Industriegewerkschaft
INSERM	Institut National de la Santé et de la Recherche Médicale
MIT	Massachusetts Institute of Technology
NASA	National Aeronautics and Space Administration
NIH	National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
PCR	Polymerase chain reaction
R&D	Research and Development
RCT	Randomized clinical trial
SSIC	Swiss Science and Innovation Council
UCSF	University of California San Francisco
US	United States

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