Between Clinical Medicine and the Laboratory: Medical Research Funding in France from 1945 to the Present

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Abstract. By focusing on funding methods, this paper considers the way in which medical research eventually led to the science-based medicine that is prevalent in France today. This process seems to have taken place in three stages during the second half of the twentieth century. In the 1940s and 1950s, two major events occurred. The first was the creation of a national health insurance fund in France, which opened up new reasons for, and ways of, funding medical research. The second was the development of antibiotics, which triggered a revival of clinical medicine. In the 1960s and 1970s, a proactive government science policy allowed the life sciences and medical research to come together in the wake of a burgeoning new science: molecular biology. Thus, in 1964, the creation of the National Health and Medical Research Institute (Institut national de la santé et de la recherche médicale or INSERM), destined to "molecularize" medical research, was seen as the fulfillment of the government's ambitious research policy. Today, with medicine irreversibly embedded in scientific and technical rationality, health has become a major issue in modern societies. This paper therefore touches on some of the key features of biomedical research, including the revival of funding systems for clinical research and the development of a system of research grants that was made possible by patient organizations and the creation of new

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funding agencies. ***Keywords:*** France, biomedicine, medical research, research endowment, INSERM.

In France, until recently, the development of medicine has followed two distinct paths. These two paths have now come together to create present-day science-based medicine. The first path, exemplified by early nineteenth-century clinical medicine—i.e., the practice of hospital medicine—focused on perfecting diagnostic techniques and developing exploratory tools such as the Laennec stethoscope and autopsies. This is how clinical medicine came to establish anatomical pathology, a descriptive science that sanctioned a holistic conception of medicine. Although it established for a century the world-wide reputation of the Paris Clinical School, including in North America, the development of clinical medicine reduced the scope of activities of hospital laboratories to so-called complementary examinations serving as an endorsement of clinical empiricism.[1] The other path of medical development, that of laboratory medicine, is based on the approach to the life sciences, such as bacteriology or biochemistry, that emerged at the end of the nineteenth century in scientific institutions such as the Pasteur Institute (Institut Pasteur) in Paris. In these institutions' laboratories, biologists developed vaccination, paving the way for preventive medicine as the main driver of medical progress. This motivated the implementation of a national health insurance scheme, as well as the direct intervention of the Rockefeller Foundation in medical research and public health organization in France.

Established in 1913 by John D. Rockefeller, Sr. and his son, the Rockefeller Foundation was initially primarily devoted to the modernization of medicine in North America. Soon, however, it extended its field of activity worldwide. France was one of the main beneficiaries of Rockefeller philanthropy between the two World Wars, especially in the field of public health. This included

1. See, for instance, Thomas N. Bonner, *Becoming a Physician: Medical Education in Great Britain, France, Germany and the United States, 1750–1945* (Oxford and New York: Oxford University Press, 1995) and George Weisz, *The Medical Mandarins: The French Academy of Medicine in the Nineteenth and Early Twentieth Centuries* (Oxford and New York: Oxford University Press, 1995).

support for the first major French institution combating tuberculosis (the Office national d'hygiène sociale) as well as for clinical medicine. An effort in the beginning of the 1930s to introduce a reform of university hospitals in Paris, as had been done in the United States at the Johns Hopkins and in Great Britain, was unsuccessful primarily because of the conservatism of the French medical profession.[2]

Therefore it was not until the end of the twentieth century that the two separate paths of the clinic and of the laboratory eventually converged in France, thanks to implementation of a new government research policy. In the field of clinical medicine, exploratory methods were developed using imaging techniques (ultrasounds, scanners, magnetic resonance imaging, and so on) and clinical trials, while in molecular medicine pathologies were discovered and population genetics grew as a field of study along with the widespread practice of the contemporary evidence-based medicine born in North America at the end of the twentieth century.

In this essay, we wish to focus on funding methods—public funding versus private initiatives, scientific authorities versus health authorities, and support for the biological sciences versus the development of clinical research—in order to consider the ways in which medical research eventually led to the science-based medicine that is prevalent today. In France, this process seems to have taken place in three stages. In the aftermath of the Second World War, while medical research was still far from being a priority in the overall research budget, two major events occurred.

The first was the creation of a national health insurance fund in France called Social Security (Sécurité sociale), which opened up new ways of funding medical research. The second was the "therapeutic revolution" (i.e., the development of antibiotics),[3] which triggered a revival of clinical medicine.[4] In the 1960s and 1970s, a

2. See Jean-François Picard, *La Fondation Rockefeller et la Recherche Médicale* (Paris: PUF, 1999).

3. This term was coined by Jean Bernard, *C'est de l'Homme qu'il s'agit* (Paris: Buchet Chastel, 1982), 17.

4. Without doubt, the history of pharmaceuticals is important and there has been much recent research by French historians on this subject. Their conclusions show, however, that although medical and pharmaceutical research is closely connected, the manner in which research is conducted is very different in the two fields. See, for instance, Jean-Paul

proactive government science policy set by a Délégation Générale à la Recherche Scientifique et Technique (DGRST) allowed the life sciences and medical research to come together in the wake of a burgeoning new science: molecular biology. Thus, in 1964 the creation of the National Health and Medical Research Institute (the Institut national de la santé et de la recherche médicale or INSERM), destined to "molecularize" medical research, was seen as the fulfillment of the government's ambitious research policy—as a success story of "scientific Colbertism." Today, with medicine irreversibly embedded in scientific and technical modes of thought, health has become a major issue in modern societies. In this paper, we therefore wish to emphasize some of the key features of biomedical research, including the revival of funding systems for clinical research and the use of research grants that was made possible by the efforts of patient organizations and the creation of new funding agencies.[5]

1945–58: PUBLIC HEALTH AND RESEARCH FUNDING

After the Second World War, the concept of "biomedicine" began to emerge in the English-speaking scientific world. In France, however, medical research continued along two separate paths. These left little room for contact between the clinical medicine inherited from the nineteenth century, which favored the study of pathological cases, and laboratory research, which promoted the preventive medicine often deliberately ignored by clinical medicine.

Gaudillière, "Une Marchandise Scientifique? Savoirs, Industrie et Régulation du Médicament dans l'Allemagne des Années Trente," *Ann. Econ. Soc. Civilis,* 2010, *65*, 89–120.

5. For further reading on the funding and organization of French medical research, see Laurence Schaffar, "Associations, fondations et recherche publique," in *Organisation de la recherche et conformisme scientifique*, ed. Alain Esterle and Laurence Schaffar (Paris: PUF, 1994); Laurence Esterle and R. Barré, "La Recherche Publique dans le Domaine Biomédical en France," in *La recherche et l'innovation en France*, ed. Jacques Lesourne and Denis Randet (Paris: Odile Jacob, 2008); Jean-Paul Gaudillière, *Inventer la Biomédecine: La France, l'Amérique et la Production des Savoirs du Vivant, 1945–1965* (Paris: Éditions la Découverte, 2002); Jean-François Picard and S. Mouchet, *La Métamorphose de la Médecine: Histoire de la Recherche Médicale dans la France du XX Siècle* (Paris: PUF, 2009); and Jean-François Picard, "Funding French Medical Research in les Trente Glorieuses and After," Paper presented at ICHST Budapest, 2009, at http://www.vjf.cnrs.fr/histrecmed/publications-electroniques/funding-french-medical-research/funding-french-medical-research.html (accessed 31 August 2010).

Yet, during the same period, the field of health care underwent profound changes with the implementation of a national health insurance scheme.

After the war, France embarked on a major reconstruction effort financed by the Marshall Plan to modernize the country's economic base under the Monnet Plan. At the same time, the government created the Social Security system to pay for health care. The Laroque Ordinances of October 1945 brought the scheme into being and provided for its funding through a system of deductions at source (from workers' salaries and employers' Social Security contributions). In contrast to Great Britain's National Health Service which was financed by a tax and had difficulty in establishing its funding base, Social Security in France quickly had funds because of unused reimbursements for medical care which could be spent on research.[6] This called into question the relationship between social medicine and medical research. Before the war, parliamentary debates on the implementation of national insurance schemes had already revealed the desire to provide the working class with access to recent medical progress in screening for tuberculosis, vaccination, and more. Yet, in 1928, during the discussion in the Parliament about a first version of a Social Security bill, the deputy Dr. Edouard Grinda argued that such a scheme could bring to the working class the medical progress it needed: "There are too many dead because of diseases in the country of Pasteur where medical science is so brilliant. So, with this new bill you will discuss, the matter is the settlement of a new medicine from which everybody should benefit."[7] Then, in 1941, with the support of the Rockefeller Foundation, the Health Ministry created a National Hygiene Institute (the Institut National d'Hygiène or INH), the forerunner of the INSERM, to implement health policy in response to the events taking place (epidemiology, food rationing, and so on).[8] In the aftermath of the war, with its first available

6. L. Berlivet, "Les Médecins, le Tabagisme et le Welfare State: Le Gouvernement Britannique Face au Cancer (1947–1957)," *Ann. Econ. Soc. Civilis,* 2010, *65*, 157–90.

7. Philippe Olivera, "Loi sur les assurances sociales du 5 avril 1928, Travaux parlementaires, Guide pour les recherches sur les travaux parlementaires concernant les assurances sociales de 1919 à 1928" (1993) available at: http://www.histrecmed.fr/documents-archives/assurances-sociales.html (accessed 13 August 2010).

8. Jean-François Picard, "Aux Origines de l'INSERM: André Chevallier et l'Institut National d'Hygiène," *Sci. Soc. Sante*, 2003, *21*, 5–26.

funds, the Social Security system set up a consultative committee for health studies, known as the Comité consultatif d'études sanitaires, in cooperation with the INH. Its purpose was to focus research on the issues affecting the French national health insurance system, such as infant mortality and the effectiveness of the BCG vaccine. It also supported certain projects such as establishing a national blood transfusion center.

One new medical procedure was testing for incompatibility of the Rhesus factor between the mother and child, following the discovery of the factor in America by Philip Levine, Alexander S. Wiener, and Karl Landsteiner during the war. Maternal–fetal incompatibility of this blood type antigen produced several thousand miscarriages a year, and when Marcel Bessis at the Saint Antoine Hospital in Paris began offering a prenatal test for the blood type compatibility of couples, he was soon doing 500 tests a month. This was one of the first procedures reimbursed by the new Social Security fund. When the Ministry of Health received an annual budget request from the transfusion service at Saint Antoine for 500 million francs, which was equal to all funds devoted to health in the country, it was decided in 1949 to create a National Blood Transfusion Center (CNTS), which subsequently became very important for immunological and hematological research.

The other major event of that time was the discovery and diffusion of the first antibiotic drugs by biochemical laboratories. Sulfonamides were first discovered by chemists at IG Farben in Germany, and then in the "therapeutic chemistry laboratory" of the Pasteur Institute, while penicillin, whose therapeutic efficacy was discovered in Britain and whose mass production techniques were developed in the United States during the Second World War, was introduced in France just after the war through one of the scientific committees based at the National Centre for Scientific Research (the Centre National de la Recherche Scientifique—CNRS).

At the outbreak of the Second World War, Gustave Roussy, the former Dean of the University of Paris Medical School, had been involved in the establishment of the French CNRS, the new public research organization in charge of coordinating academic science research, and he subsequently created an Experimental Medicine Commission. Despite Roussy's efforts, this commission was unsuccessful in achieving its goal of coordinating all government research

in France because its activities were largely separated from graduate education and especially from the medical schools in which medical research was mostly absent. As a result in 1944 when the CNRS was reorganized, it set up a committee on antibiotics (Commission des antibiotiques) headed by the Pasteurian André Lwoff, but no clinicians were included. In fact, the unobtrusive role of doctors in medical research led Lwoff to advocate "demedicalization." In a letter to the head of the CNRS, he wrote:

> If medical research is to be reorganized, the scientific study of human infectious diseases cannot be treated as part of the field of medicine. Microbiology was developed in laboratories and multi-disciplinary institutions, which made it possible to solve problems pertaining to protein structures and to combine research on infectious pathologies and genetics. The fact that in France microbiology is taught not in science faculties but in medical faculties, by professors who are not specialists, has led to a very serious crisis in the discipline.[9]

This can explain why in 1947 a government report revealed just how poorly funded French medical research was. Indeed, it received only a meager share of the 1.2 billion Old Francs devoted to all the life sciences.[10] This included the budget of the Pasteur Institute (one billion Old Francs), which confirmed the importance of the institution, but research at the Pasteur Institute was beginning to move in the direction of molecular genetics, a field not preoccupied by medical concerns. In the CNRS budget of the time, it is impossible to quantify the share of the life sciences budget (200 million Old Francs) devoted to medical research, but in any case it remained very small. In 1947, the organization had only one laboratory for experimental medicine, the Gustave Roussy Institute for Oncology, and was awarding only a few individual fellowships in this field.

9. Steering Committee for Medical Research at the CNRS. Note A. Lwoff (December 1944), CNRS Archives, AN 20-284, 212.

10. The data are given in Old Francs (OF) until 1960; thereafter the New Franc (NF), worth OF 100, was introduced. The New Franc was replaced on 1 January 1999 by the Euro, worth NF 6.56. To compare some of the data taking buying power into account, a conversion was made to present the data in 2007 Euros. The conversion was made using INSEE coefficients, available at: http://www.insee.fr/fr/indicateurs/indic_cons/pouvoir_achat.pdf (accessed 13 August 2010).

As for the INH, its small budget was less than half a million 1947 francs. Even though the institute benefited from U.S. aid that enabled Louis Bugnard, its director, to set up a generous fellowship scheme for medical researchers, when addressing the Social and Economic Council in 1953 he spoke of the deplorable financial precariousness of French medical research: "where France has a Franc available, 90 Francs are spent in Great Britain and 1,000 in the United States."[11]

However, faced with the weaknesses of funding for medical research and the small budget of the INH, a new generation of clinicians, including hematologist Jean Bernard, nephrologist Jean Hamburger, and allergy specialist Bernard Halpern, refused to be ousted from their positions in charge of research. As the spread of antibiotics sidelined the fight against infectious diseases—for example, the use of streptomycin against tuberculosis—neo-clinicians made clear their intention to tackle chronic diseases such as cancer, cardiovascular diseases, allergies, and nephritis, and set about acquiring the means to do so. In the early 1950s, the Assistance publique-Hôpitaux de Paris (AP-HP), the central Parisian hospital administration under which their hospitals were placed, agreed to establish the Association Claude Bernard (ACB) funded by the City Council of Paris and the Regional Council of the Seine, to help set up research laboratories in their hospitals.[12]

Following this initiative, French medical research finally took off, thanks to the financial commitment of the health authorities—the INH, the ACB, and the national health insurance fund—and of the public research organization—the CNRS.[13] In 1957, with a budget of just under one billion Old Francs, about twenty laboratories were set up that were soon to become the first research units of the future INSERM. With regard to the Pasteur Institute (1.5 billion Old Francs), which remained one of the most important actors in the field, it is worth pointing out the large-scale development of an

11. L. Bugnard, Hearing by the Social and Economic Council, 16 January 1953, INSERM Archives, AN 2006-293.

12. In fact, the Association Claude Bernard also stemmed from the Association pour la recherche médicale created by Louis Pasteur-Valléry-Radot and Jean Hamburger in 1948, later transformed into the Fondation pour la Recherche Médicale. See Picard and Mouchet, *La Métamorphose*, 102–21.

13. Cooperation between the CNRS and the INH was facilitated by the fact that Bugnard, head of the INH, was appointed president of the Commission for Experimental Medicine at the CNRS.

activity that was indirectly linked to research: the industrial production of vaccines (BCG, DTaP-IPV, and others). The total public budget devoted to medical research reached more than 2.3 billion Old Francs.

Finally, in 1958, inspired by the forty-year-old reforms of the Rockefeller Foundation in the United States, which followed Flexner's model of uniting care, teaching and research in medicine, and thanks to significant support from the Ministry of Health, Professor Robert Debré established a group of university hospitals—the Centres hospitalo-universitaires (CHU)—with the goal of providing medical students access to hospitals by creating a body of full-time university hospital professors. Yet, in spite of the firmly asserted principles, medical research remained somewhat neglected, due to a lack of specific funding from the Ministry of National Education for the medical faculties that relied on it.[14] But the advent of the Fifth Republic and concerns expressed by General de Gaulle over national independence triggered a proactive science policy from which medical research was to benefit greatly.[15]

1958–80: THE FIFTH REPUBLIC SUPPORTS MEDICAL RESEARCH

The new Republic's main goal was for France to take its appropriate place between the two Cold War blocs. This included meeting the urgent need, identified by the Commissariat au Plan (the State Planning Commission), to renew the link between basic scientific research and the needs of a society undergoing rapid economic expansion. A new administrative office for scientific research created in 1958, the Délégation Générale à la Recherche Scientifique et Technique (DGRST), was charged with this task. This organization was in fact the precursor of the Ministry of Research, in charge of sharing out the research budget between the main scientific institutions. The other decisive events in this scientific reorganization were the breakthroughs in the life sciences, highlighted by a series of Nobel Prizes—including those of the three Pasteurians, André Lwoff, Jacques Monod, and François Jacob (1965)—which clearly

14. In spite of the first specifications of the Ordinance of 30 December 1958, it reflected Robert Debré's desire to bring higher education closer to clinical medicine, rather than Jean Dausset's wish to promote medical research. Picard and Mouchet, *La Métamorphose*, 128–30.

15. Alain Larcan and Jean-François Lemaire, eds., *De Gaulle et la Médecine* (Paris: Synthélabo, 1995), 1–8.

contributed to turning the tide of funding toward medical research. Paradoxically, in these new settings, physicists rather than biologists played a crucial role in decisions regarding the main directions of scientific inquiry. Pierre Auger, a well-recognized scientist in nuclear physics who had a major role in the building of the French atomic agency, in a programmatic report asked for by the DGRST, advocated prioritizing the development of molecular biology, the medical applications of which were already being foreseen. Auger wrote:

> Molecular biology includes the different aspects of research on the composition and role of biological macromolecules, DNA, proteins, enzymes, on their functions for reproduction and in the metabolism, and on the way they combine inside cells. A very fruitful synthesis is taking place between the doctrines of biochemistry, biophysics and cellular physiology around the concept of the macromolecule, which is likely to generate interest from the field of genetics, radiobiology and cellular differentiation. Aging and cancer are also closely related to this field, which is one of the main trends in biology, one of the most active as well as one of the promising for the future.[16]

From 1961 to 1966, the DGRST budgeted 251 million New Francs (the equivalent of €350 million in 2007) for the life sciences and 234 million (€325 million) for medical research—in other words, close to half a billion New Francs (€700 million) over five years. This corresponded to half of the national research budget for all sciences.[17] Following the example of the U.S. scientific world, the DGRST also introduced another major innovation by making grants for scientific research. By acting as a funding agency (i.e., an organization that does not actually own laboratories, but has the financial resources necessary to direct their activities through grants, as the National Science Foundation in the United States does), the DGRST was able to increase funding for scientific fields that were seen to have been insufficiently developed until then. It should be noted that half of the first set of ten concerted actions launched in

16. "Rapport Général sur la Situation Présente et l'Action à Envisager dans le Domaine de la Biologie Moléculaire," Comité d'Études Biologie Moléculaire, March 1960, cited in X. Polanco, "La Mise en Place d'un Réseau Scientifique, les Rôles du CNRS et de la DGRST dans l'Institutionnalisation de la Biologie Moléculaire en France (1960–1970)," *Cahiers pour l'Histoire du CNRS,* 1990, *7*, 1–24.

17. "Situation et Perspectives de la Recherche Biologique et Médicale Française," *Le Progrès Scientifique* (April 1965), *83*, 1–32.

TABLE 1

Projects for the Distribution of Funds for Concerted Action in MNF (1963)*

Concerted actions	Amount in millions of current New Francs
Energy conversion	28.2
Ocean exploration	39.6
Molecular biology	27.2
Cancer and leukemia	19.2
Brain functions and diseases	4.9
Genetic applications	2.8
Animal and human nutrition	3.7
Demographic, economic and social analysis	3.0
Economic sciences and development issues	4.6
Miscellaneous and urgent actions	10.5
Total	143.7

MNF, millions of New Francs.
*DGRST Archives, Fonds de Développement, 4 October 1963, 449-041063.

1960 related to the life sciences and their funding (NF 57.8 million), accounting for 40 percent of the total spent on research (Table 1).

Apart from the shortcomings of the 1958 university hospital reforms mentioned above with regard to medical research, the DGRST noted that the old INH had difficulties managing the new funds available in the government research budget. In June 1959, an administrative reform commission was set up to critically assess the running of the organization. One of the conclusions of the report was that the Institute had been unable to solve the issue of doctors holding several posts concurrently (in 1960, the wages bill made up about 75 percent of the INH budget). This had resulted in numerous cases of fraud, which were denounced by the fiscal authorities.[18] The running costs of the INH also appeared

18. With regard to recruiting doctors, the INH was penalized from the start by the ban on the accumulation of salaries linked to public sector posts (of the 350 researchers who worked at the INH from 1946 to 1955, 300 were doctors who then went back to working in a practice). In other words, doctors who chose to pursue a career in research impeded

disproportionately high: they were 14 percent of the organization's budget, whereas such costs did not exceed 2 percent of the budget of the CNRS. Talks between the different authorities led them to consider shutting down the INH, entrusting the CNRS with its laboratories,[19] and bringing its teams of epidemiologists directly under the Ministry of Health.[20]

However, supported by hospital clinicians, the Ministry of Health was loath to relinquish its prerogative over medical research. Instead, cancer specialist Georges Mathé, an adviser to the Health Minister, suggested that the INH be transformed into "a genuine research institution."[21] This idea was ratified by the decree of 18 July 1964, which announced the creation of a new national health and medical research institute, the INSERM. Inspired by the British Medical Research Council (MRC) and the U.S. National Institutes of Health (NIH), the INSERM was charged with aligning laboratory and clinical research more closely, but in a manner that followed the direction of the French centralized government more than its Anglo-Saxon counterparts followed their respective governments. With substantial funding, the budget for medical research almost tripled, from twenty-eight million New Francs in 1962 to seventy-two million in 1966. The structure of the scientific council of the INSERM and its division into thirteen specialized scientific commissions highlighted the new priority given to cellular and molecular pathologies, genetics, cell physiology, and other similar fields. This institution was furthermore called upon to take over the concerted actions of the DGRST, which were soon to be followed by planned programs around particular research themes, or

their capacity to generate revenue, in comparison with their colleagues who were free to practice as independent general practitioners. Hence the accusations of fraud when these rules were by-passed. In fact, the issue of medical researchers' pay and the insufficiency thereof has been central to the INH from its creation in 1941 up to 2000 when a contractual policy was implemented by the head of the INSERM.

19. In the first decade of the twenty-first century, the CNRS, in charge of developing fundamental research in all scientific fields, spent about 25 percent of its budget on the life sciences.

20. Commission de Réforme Administrative 1959, Rapport no 4, Education Nationale, 2 June 1959. DGRST Archives, batch 660.

21. J.-P. Gaudillière, C. Rigal, S. Mouchet, and J-F. Picard, Compilation of several interviews with Georges Mathé, 27 September 1989, 5 March 1999, 13 February 2001, 26 May 2002, and 10 July 2002, available at: http://www.vjf.cnrs.fr/histrecmed/entretiens/mathe/mathe.html (accessed 13 August 2010).

"actions thématiques programmées" (ATP), in priority fields such as immunology, pharmacodynamics, and health economics. In 1965, the DGRST carried out its first assessment of the reforms: whereas in 1960 funding for French medical research was equivalent to no more than a seventh of its British counterpart, five years later it had reached a quarter.[22]

Under the impetus of the INSERM and the CNRS, molecular biology and medical research merged through the development of biotechnologies.[23] The most significant success of this confluence of fundamental research and medical research was the advent of immunology.

In 1980, the French researcher, Jean Dausset was awarded the Nobel Prize in Physiology or Medicine with the American researchers Baruj Benacerraf and Georges Snell for the discovery of the human leukocyte antigen (HLA). The boom in immunology and cancer research also led to the creation of new institutions: the Institut Cochin de génétique moléculaire in Paris (Jean-Paul Lévy); the Institut de cancérologie et d'immunogénétique in Villejuif (Georges Mathé); the Institut de génétique et de biologie moléculaire et cellulaire in Strasbourg (Pierre Chambon); and, the Centre d'immunologie de Marseille-Luminy (Michel Fougereau and F. Kourilsky).

The way in which the INSERM budget was distributed among the main lines of research revealed the new importance given to basic research. Looking at the doubling of the INSERM annual investment budget by field of activity (from twenty-five to fifty million New Francs from 1971 to 1975), we find that as funding for cancer research and molecular biology doubled, funding tripled for immunology.[24] A first attempt to internationalize medical research was also seen in the establishment of organizations such as the International Agency for Research on Cancer (IARC) in Lyon and the European Organization for Research and Treatment of Cancer (EORTC), and with France's participation in the U.S. National Cancer Program (from 1971 to 1976, with thirty-one million francs budgeted by the INSERM). Of note in the area of scientific

22. "Situation et Perspectives de la Recherche Biologique," 1–18.
23. Gaudillière, *Inventer la biomédecine*, 9–10.
24. INSERM Archives, AN 2006-283.

review, the INSERM seeks to follow international standards of evaluation of research, something new in French medical history. One reflection of this is the encouragement of French researchers to publish their results in English, and for their work to be included in American research databases like Medline.

These efforts were not enough, however, to shield the INSERM from criticism, especially for being too far removed from the concerns of clinical medicine.[25] It had to deal with Georges Mathé's reproaches after a project shed light on the medical profession's capabilities (admittedly traditional) for fundraising among the public, especially among patients. With the help of the CNRS and in spite of resistance from the INSERM, in the early 1970s, Professor Mathé launched a cancer research foundation, the Association pour la Recherche sur le Cancer (ARC) in Villejuif as a vast fundraising project. In 1974, its budget already amounted to ten million francs (the equivalent of €7 million in 2007); 4.6 million came from calls for subscriptions among the public and three million from bequests and donations given by patients' families. These funds allowed the ARC to provide the various research institutions in the Villejuif area with significant support.[26] At the beginning of the 1980s, the funds collected by the ARC reached close to twenty million francs (the equivalent of €14 million in 2007). Other actors in the field, such as the National Cancer League, the Federation of Cancer Centers, and the Curie Institute began to accuse the ARC of draining the resources available for the fight against cancer.[27] The Association was eventually charged with

25. "Projet de Rapport sur la Démédicalisation de l'INSERM," Report of the Scientific Council, 1–2 March 1976, INSERM Archives file 9440.

26. The Institute for Scientific Research on Cancer (Institut de Recherche Scientifique sur le Cancer, or IRSC) that depended on the CNRS was allocated 1.8 million francs (the equivalent of 1.2 million Euros in 2007), the Gustave Roussy Institute (IGR) was allocated 1.2 million francs (0.8 million Euros) as was the Cancer and Immunogenetics Institute (Institut du Cancer et d'Immunogénétique, or ICIG), and the radiobiology department at the Paul Brousse hospital was allocated 0.4 million francs (0.3 million Euros). ARC, Report of the Scientific Council, 7 November 1974. Yet even with such large amounts, in October 1975 Georges Mathé spoke out against Simone Veil, the Minister of Health, reproaching her for having declared that "this disease was not a priority for medical research." INSERM Archives, AN 2001-165.

27. At the end of the 1970s, the National Cancer League (Ligue Nationale Contre le Cancer) had a budget of 6.2 million francs, the Federation of Cancer Centers (Fédération des Centres Anticancéreux) a budget of thirteen million francs, and the Curie Institute a budget of 1.2 million francs. INSERM Archives, "Cancer" folder, AN 2006-283.

embezzlement at the end of the 1990s. After a sensational trial, some of its leaders were sentenced to prison and the General Inspectorate of Social Affairs, i.e., the Ministry of Health, took the organization back under its authority.

1980 ONWARDS: THE EXPANDING WORLD OF MEDICAL RESEARCH

With the election of President François Mitterrand in 1981, and the installation of a socialist government, a research ministry, the Ministère pour la Recherche et la Technologie (MRT) was created to be in charge of the entire civil budget for research and development. The French government also designated established public research organizations (CNRS, INSERM) as public scientific and technological institutions—Etablissement public à caractère scientifique et technologique (EPSTs). This meant that employees of these institutions had the status of civil servants. With the INSERM under the supervision of the Ministry of Research, its ties with the Ministry of Health began to weaken. Its relationships with the universities, which were not affected by the reforms and were still dissociated from research, remained limited.

In 1982, Philippe Lazar was appointed managing director of the INSERM. In the same spirit as his predecessors, he sought to establish a policy of excellence in research, based on the refusal to program research and the safeguarding of researchers' freedom. Another significant change in the INSERM was the massive influx of biologists, biochemists and some researchers from the social sciences at the expense of physicians, as a result of granting tenure to full-time researchers.[28]

Yet, while the INSERM maintained steady expansion with a budget that increased from 100 million francs in 1964 to 600 in 2005 constant francs, its policies did face some difficulties. First, the priority given to fundamental research continued to marginalize clinical research. Second, the refusal of the institution's senior management to endorse any kind of scientific programming impeded its ability to address issues concerning emerging pathologies and rare

28. Article by P. Lazar published in the *Comptes Rendus de l'Académie des Science*, in the section *La Vie des Sciences*, for the tenth anniversary of the INSERM (Paris: INSERM, 1984).

diseases. In view of this, new investigators were entering some neglected fields of public research, while hospital medicine became eager to revitalize clinical research. At the beginning of the 1980s, the AIDS epidemic and the development of medical genomics on rare diseases reveal these changes.

Two years after the AIDS virus was discovered in 1983 in a laboratory of the Pasteur Institute (research which resulted in the Nobel Prize in Physiology or Medicine being awarded in 2008 to Françoise Barré-Sinoussi, and Luc Montagnier from the Pasteur Institute and to the German Harald zur Hausen for the discovery of the role of papilloma virus in uterine cervix cancer), the INSERM still had no specific funds to support research in this field.[29] It was not until 1987 that it agreed to a more proactive policy under pressure from the Ministry of Health, and set up a national AIDS research program with a budget of 100 million francs (€22.5 million, 2007) from the Ministry of Research. After further government intervention, this program led to the creation of a French national agency for AIDS research, the Agence Nationale de Recherches sur le Sida (ANRS), a public interest group created in 1992 to manage the different initiatives for AIDS research. This new agency has been able to fund research in various fields (biology, clinical medicine, vaccine science, therapeutic sciences, epidemiology, social sciences, etc.), thanks to substantial funding: the equivalent of €32 million in 1989 and close to €50 million in 2007. The French agency claims its financial effort on AIDS is equal to half of the whole U.S. budget for AIDS research. As it benefits from more flexible management than the public institutions that enable it to provide grants for research and post-doctoral projects, the ANRS has been able to introduce original forms of partnership, on the one hand with civil society for clinical trials and on the other with the pharmaceutical industry for vaccine research. One of ANRS's strong points has been its ability to structure clinical

29. When the AIDS epidemic reached France in the early 1980s, mobilization first began with a group of young clinicians who spontaneously cooperated with a laboratory of the Pasteur Institute that was associated with the CNRS. This allowed for the infectious agent to be isolated and identified as early as 1983. Jean-Francois Picard and Martine Bungener, "Quelles Recherches pour le SIDA?" Memorandum presented to the general management of the INSERM, 1991, available at: http://www.histrecmed.fr/publications-electroniques.html (accessed 13 August 2010).

research on AIDS, which has led it to strongly support therapeutic trials using procedures still seldom developed in France.[30]

Medical genomics was another field that received insufficient attention from public research. In the 1980s, when the advent of biotechnologies made it possible to analyze the genome of living beings, the Human Genome Project became a major scientific priority in the United States.[31] In France, however, biologists at the CNRS were wary of what they perceived as little more than an industrial project, far removed from the concerns of fundamental research.[32] This is why one of the first mappings of the human genome came from 1980 Nobel Prize-winner Jean Dausset's Center for the Study of Human Polymorphisms, the Centre d'étude du polymorphisme humain (CEPH), a private medical foundation.[33] The French muscular dystrophy organization, the Association Française contre les Myopathies (AFM), a dynamic charity foundation, soon took over from the CEPH and contributed to the reconfiguration of the medical research world by making itself a key player in the field of genomic research.[34]

In 1987, a year after the discovery of the Duchenne myopathy gene, the AFM launched its own Téléthon on the model of its U.S. equivalent, the Muscular Dystrophy Association's annual telethon. It raised considerable funds through this event (close to the equivalent of €30 million in 1987, over €100 million in 2004) and dedicated a substantial share of this money to research. With these resources and a more flexible management than the public research laboratories (EPSTs), the AFM was able to steer researchers toward questions of disease etiology and genetic disease therapy. At the same time, it also developed a pool of young researchers by sponsoring numerous Ph.D. students and post-doctoral researchers in public laboratories. The AFM proved keen to give grants to projects

30. *10 Ans de Recherches sur le SIDA en France, 1988–1998* (Paris: ANRS, 1998), 1–36.

31. Jean-Paul Gaudillière, "Le Vivant à l'Heure de la Génomique," *La Recherche*, 2000, *329*, 54–58.

32. S. Mouchet and J.-F. Picard, Interview with Axel Kahn, 27 February 2003, available at: http://www.histrecmed.fr/entretiens/kahn/kahn.html (accessed 13 August 2010).

33. The CEPH was created in 1982 by Jean Dausset and Daniel Cohen. N. Givernaud and Jean-Francois Picard, "Histoire de la Génomique en France," available at: www.histcnrs.fr/Histgen.html (accessed 13 August 2010).

34. N. Givernaud and J.-F. Picard, Interview with Bernard Barataud, 7 June 2001, available at: http://www.histrecmed.fr/entretiens/barataud.html (accessed 13 August 2010).

deemed too innovative and risky by big public institutions and, like other smaller charities, it favored preclinical trials, thereby making up for some of the shortcomings of public research. Of the 740 million francs devoted to research on the human genome between 1988 and 1991 (excluding public researchers' salaries), 500 million came from the AFM. In the early 1990s, it acquired its own research competencies with the creation of the Généthon, a center for research on the human genome, in Evry. This organization made a name for itself with the first worldwide exclusive mapping of the human genome. From 1995, it devoted its activity to exploiting that achievement in order to help patients, and later turned toward gene and cellular therapy to provide therapeutic treatments for rare diseases. In 1998, the Généthon became part of Genopole, a scientific interest group based in Evry, which also includes a national sequencing center, the Centre national de séquençage (or Genoscope directed by Jean Weissenbach) and a national genotyping center.[35] While the Généthon currently hosts researchers and laboratories from various research organizations (INSERM, CNRS, and so on), its budget, excluding tenured staff, mostly consists of AFM funds (close to 90 percent of the €22 million in 2007).

Another important event in recent decades is the comeback of clinical research. We have already seen how the molecularization of medical research that began in the 1960s and 1970s, when the INSERM was created, contributed to marginalizing the type of research relevant to clinical medicine. Unlike the British Medical Research Council or the American National Institutes of Health that also act as funding agencies, the INSERM is a research operation that manages its own staff and devotes almost all of its funds to its own laboratories (over 300 in the years after 2000). As its wage bill takes up two-thirds of its budget, little is left to support outside research projects (less than 3 percent in 1993). To remedy this situation, in the early 1990s a delegation for clinical research was set up under the umbrella of the Parisian hospital administration, the Assistance publique. A program for clinical research in hospitals, the Programme hospitalier de recherche clinique (PHRC) was then

35. N. Givernaud and J.-F. Picard, Interview with Pierre Tambourin, June 2000–November 2001, available at: http://www.vjf.cnrs.fr/histrecmed/entretiens/tambourin/tambourin.html (accessed 12 August 2010).

launched, with a budget equivalent to €21 million in 1995. This grew to €50 million ten years later. At the initiative of the INSERM and the Assistance publique (AP-HP), the first clinical investigation centers, the Centres d'investigations cliniques (CIC), were created to bring research closer to the bedside ("translational" research) and to develop therapeutic trials in hospitals. The proponent of these reforms, Professor Pierre Corvol of the Collège de France, recalled:

> Clinical research in France suffered from an inadequate hospital infrastructure, notably because the French hospital system favors the autonomy of clinical services. This works against the creation of collaborative efforts such as are found in the departments of the big North American university hospitals. In November 1989, we therefore proposed an agreement which was signed by the INSERM and the directors of the hospitals of Paris. It was the director of the "Assistance publique-hôpitaux de Paris" (AP-HP), in the name of better compliance in presenting the results of research done together by researchers and clinicians, who suggested the name "Clinical Investigation Center" (Centre d'investigation clinique or CIC) rather than "CRC" (clinical research center) used in the United States and which the French hospital administration feared.[36]

Then, after 2000, several measures were taken concerning hospitals. One of these was the reform of activity-based costing implemented by the Ministry of Health in 2002, which brought clinical research back in the game with the creation of an endowment for teaching, research, and innovation projects, called the Missions d'enseignement, de recherche, de référence et d'innovation (MERRI). Almost eighty hospitals now benefit from "MERRI" funds, including all the university hospitals and cancer centers. The aim of MERRI funds, which are provided by the Ministry of Health and included in the hospital budget, is to cover the extra costs incurred through the allocation of medical time to research and teaching, as well as through the use of hospital facilities for research.[37] In 2007, MERRI funds amounted to

36. S. Mouchet and J.-F Picard, Interview with Pierre Corvol, 13 May 2002, available at: http://www.vjf.cnrs.fr/histrecmed/entretiens/corvol/corvol.html (accessed 12 August 2010).

37. This funding system is complex: it consists of a set share, a flexible share based on performance indicators, and a variable contractual share for specific projects, such as funding clinical investigation centers, some of the projects covered by the PHRC, etc.

2.2 billion Euros in total (almost as much as the budget allocated to medical research). Their set shares and flexible shares together account for 1.6 billion Euros, but it is difficult to determine what proportion of these funds corresponds to actual research activities.[38] In 2007, €163 million was specifically dedicated to clinical research activities and to medical activities labeled "innovative and experimental."[39] The biggest share of funding dedicated to actual research (46 percent of the €163 million) was to support organizations such as the clinical investigation centers, which are present in almost all university hospitals.

It is understandably difficult to summarize the current state of French research which is in the midst of change. Today those institutions funding research such as the INSERM or the CNRS seem less able to respond to medical research needs than they did in the 1960s when research took off. Among the problems is that between 60 and 70 percent of the budgets of these institutions (€900 million) covers the salaries of permanent staff. This limits the turnover of researchers needed for innovation in the laboratory and the capability to answer new societal needs. In parallel, the CNRS and the INSERM laboratories took in a growing number of teacher-researchers from universities where they are usually located.

This explains the growth of new agencies that act as funding sources and do not actually have their own laboratories, but rather support and direct those who do. These entities compensate for the shortcomings of government institutions, and focus on specific diseases such as AIDS, cancer, and genetic diseases but also focus on emerging diseases (e.g., those due to prions, H1N1 virus, etc.). The lack of fixed costs of the new agencies gives them the freedom to fund new operations and thus to play a strategic role in guiding medical research.

It can be said that some features of government organizations are beginning to stand out. The first is the wish to develop a national

38. AERES, "Rapport d'Évaluation de l'INSERM, 2008," available at: http://media.enseignementsup-recherche.gouv.fr/file/2008/84/6/Rapport_AERES-S1-INSERM2008_38846.pdf (accessed 12 August 2010); IGAS Report, "Le Financement de la Recherche, de l'Enseignement et des Missions d'Intérêt Général dans les Établissements de Santé, 2009," available at http://www.ladocumentationfrancaise.fr/rapports-publics/104000024/index.shtml (accessed 31 August 2010).

39. Ministère de la Santé, de la Jeunesse, des Sports et de la Vie Associative, Rapport au Parlement sur les Missions d'Intérêt Général et l'Aide à la Contractualisation des Établissements de Santé, 2008, available at: http://www.sante-sports.gouv.fr/missions-d-interet-general-et-a-l-aide-a-la-contractualisation-migac.html (accessed 31 August 2010).

research strategy and a planning mechanism.[40] Furthermore, the CNRS and the INSERM are now divided and grouped into thematic institutes (neurosciences and psychiatry, cancer, microbiology and infectious diseases, cardiovascular and nutrition medicine, public health, biotechnologies, molecular and cellular biology, embryology and evolution, genetics–genomics–biocomputing) that aim to focus their strategy on common priorities. At the same time, more autonomy was given to universities, which were acknowledged as major actors in research.

In addition, a new National Research Agency (ANR) inspired by the U.S. National Science Foundation was created to be in charge of feeding an increasing share of the public research budget into a general granting system operated on the basis of requests for proposals.[41] Since its inception in 2004, the ANR has distributed 2.4 billion Euros. Close to 28 percent of the grant funds have gone to research in the life sciences and health. Of these funds, 24 percent were allocated to the CNRS, another 24 percent to higher education, 5.2 percent to the INSERM, and the rest to other public and private laboratories.[42] In the hands of the Ministry of Health, the Missions d'enseignement, de recherche, de référence et d'innovation (MERRI) is funding clinical research that has taken on considerable importance, and now receives 40 percent of non-recurrent public funding (163 million of 394 million Euros). As shown in Table 2, with a total of 2.5 billion Euros, medical research funding[43] currently accounts for about one-fifth of domestic expenditures on public research. In international terms, French medical research spending now corresponds to four-fifths of what is spent on British medical research. It also corresponds to a little more than one-tenth of what was spent by the U.S. National Institutes of Health in 2005, whose spending counts for more than a quarter of the whole U.S. medical research budget that includes pharmaceutical research and development.[44]

40. Jacques Lesourne and Denis Randet, eds., *La Recherche et l'Innovation en France: Futuris 2009* (Paris: Odile Jacob, 2009), 13.

41. "Recherche et Innovation en France: Surmonter nos Handicaps au Service de la Croissance," Rapport d'Information du Sénat, n 392, 11 June 2008, available at: http://www.senat.fr/rap/r07-392/r07-3920.html (accessed 12 August 2010).

42. P. Jacquet, "L'Agence Nationale de la Recherche Révolutionne la Vie des Scientifiques dans les Laboratoires," *Le Monde*, 24 November 2009, 12.

43. Excluding funding from industry, local authorities, and European and international cooperation.

TABLE 2

Estimates for Public Medical Research Funding* (2007–08)

Type of funding	Type of organization	Organization	Amount in millions of current Euros	Percent
Endowments	Public research	INSERM	492	19.9
		CNRS (life sciences)	430	17.4
	Academic	Universities (including medical faculties)	802	32.5
	Foundation	Pasteur Institute	192	7.8
	Total		***1,916***	***77.6***
Non-recurrent funding (grants)	Public agencies or equivalent	Agence nationale de la recherche (ANR)	135	5.5
		Agence nationale de la recherche sida (ANRS)	46	1.9
		Institut national du cancer (INCa)	50	2.0
		Missions d'enseignement, de recherche, de référence et d'innovation (MERRI)	163	6.6
		Total	*394*	*16.0*
	Civil society organizations	Cancer foundations (ARC and Ligue nationale contre le cancer)	65	2.6
		Association française contre les myopathies (AFM)	63	2.6

continued

TABLE 2 (*Continued*)

Type of funding	Type of organization	Organization	Amount in millions of current Euros	Percent
		Fondation pour la recherche médicale (FRM)	30	1.2
		Total	*158*	*6.4*
	Total	***552***	***22.4***	
TOTAL			**2,468**	**100**

While the Pasteur Institute is no longer the main source of funding as it was in the post-World War II period (see Table 1), it is still one of the key players in scientific advancement.

*In broad terms (medical research and research in the life sciences), excluding contracts with industry, local authorities, and the European Union.

WHAT IS THE OUTCOME?

Over the last half century, there is no doubt that French financial investment in research has been crucial in turning the medical empiricism of the nineteenth century into the technical and molecular medicine that we know today. Judging by the volume of work published, France is now one of the world's ten leaders in medical research. Admittedly, the bibliometric data available since the beginning of the twenty-first century reveals that France has gone down from the fifth to the seventh position—partly because of the progress made by some emerging countries such as China—but this does not seem to have had that much of an impact on the

44. See "Metric: Medical Research Budget in U.S. Hits $95 Billion," *Fierce Biotech*, 20 September 2005, available at: http://www.fiercebiotech.com/story/metric-medical-research-budget-in-u-s-hits-95-billion/2005-09-21 (accessed 12 August 2010). By comparison, the pharmaceutical R&D expenditures in France in 2005 were about 4 billion Euros. Indicateurs de Sciences et de Technologies, "Rapport de l'Observatoire des Sciences et des Techniques" (Paris: Economica, 2008), available at: http://www.obs-ost.fr/fr/le-savoir-faire/etudes-en-ligne/travaux-2008/rapport-biennal-edition-2008.html#c700 (accessed 12 August 2010).

reputation of French medical research.[45] Moreover, French medical research now has a greater impact: its publications are cited a little more often than they were ten years ago, and the impact index of the CNRS and the INSERM are largely above the world average.[46] France performs particularly well in the fields of immunology and microbiology, ranking fourth worldwide.[47] On the other hand, it is difficult to know with certainty how well clinical research is doing, as it is becoming increasingly intertwined with what is referred to as fundamental research. Nevertheless, the support it has received over the last half-century has undeniably helped to move the French clinic away from the scientific backwardness in which it had been stagnating at the end of the Second World War and helped to introduce it into the era of evidence-based medicine that prevails today.

Clearly, such performance has a cost. The rise in health-care expenditures is attributed to the development of an increasingly technical and hence more costly medicine, be it for prevention, diagnosis or treatment. In parallel, the cost of medical research is rising. Thus, rather than continuing to demonstrate improvement in the health of populations in developed countries as measured by the extending life expectancy (even in the most recent period),[48] the crucial problem is now the cost of health care for the whole population. More precisely, the problem is determining who should pay for the growing expense of increasingly sophisticated testing and treatments. As noted above, from its beginning in 1945, French Social Security devoted an important part of its budget to medical research. Obviously, this is no longer the case today. The rise in

45. Calculated using the available 2007 data from SCImago (SCImago Journal & Country Rank or SJR). Available at: http://www.scimagojr.com (accessed 24 November 2009).

46. The impact factor of the CNRS and INSERM was 1.4 in 2006, for a world average of 1 in "Indicateurs Bibliométriques sur la Production Scientifiques, en Sciences de la Vie, des Institutions Membres de l'Alliance Nationale pour les Sciences de la Vie et de la Santé" (AVIESAN), OST, 2009.

47. Laurence Esterle, et al., *La Recherche Publique dans le Domaine Biomédical en France. Analyse Quantitative et Eléments de Diagnostic* (Futuris, 2008), available at: http://www.anrt.asso.fr/fr/futuris/pdf/071115-RapportBiomed-VF.pdf (accessed 12 August 2010).

48. In France today, the increasing ratio is two months per year. According to the statistics for life expectancy of the World Health Organization in 2006, life expectancy in France was seventy-eight years for men and eighty-four for women, which was the fourth longest of all countries, ahead of the U.K. (seventy-six and eighty) and the United States (seventy-five and eighty).

health expenditures in the "welfare state" has not only reduced this ability to support research but also has exceeded the ability of Social Security even to cover all expenditures for health care. As a result, a tax-supported budget for Social Security became necessary in France starting at the end of the twentieth century, eventually leading to difficulties that are today reflected in discussions about health reforms in France, as in the United States. The conclusion could be that there are more economic than scientific challenges facing the evidence-based medicine that today prevails in developed countries.

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