The Private Science of LOUIS PASTEUR

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Laboratory Notebooks and the Private Science of Louis Pasteur

IN 1878, WHEN he was fifty-five years old and already a French national hero, Louis Pasteur told his family never to show anyone his private laboratory notebooks.[1] For most of a century those instructions were honored. Pasteur's notebooks—like the rest of the manuscripts he left behind at his death in 1895—remained in the hands of his immediate family and descendants until 1964. In that year, Pasteur's grandson and last surviving direct male descendant, Dr. Pasteur Vallery-Radot, donated the vast majority of the family's collection to the Bibliothèque Nationale in Paris.[2] But access to this material was generally restricted until Vallery-Radot's death in 1971, and there was no printed catalog of the collection until 1985.[3]

The Pasteur Collection at the Bibliothèque Nationale is stunning in its size and significance. It is a tribute not only to Pasteur's own awesome productivity as scientist and correspondent, but also to the tireless efforts of Pasteur Vallery-Radot, who greatly increased the size of the initial family collection by gathering additional correspondence and manuscripts by and about his grandfather from every conceivable source. There are, to be sure, other significant collections of manuscript materials by or relating to Pasteur—at the Académie des sciences and the Archives Nationales in Paris, for example, or at the Wellcome Institute for the History of Medicine in London, and at the National Library of Medicine in Bethesda, Maryland, in the United States. But the collection at the Bibliothèque Nationale is the largest and most important by far.

As now deposited in the Salle de Manuscrits at the Bibliothèque Nationale, the Papiers Pasteur includes fifteen large bound volumes of correspondence by, to, or about Pasteur. Another fifteen volumes contain lecture notes, drafts of published or unpublished manuscripts, speeches, and

related documents. Most important, the Papiers Pasteur includes a meticulously preserved collection of more than 140 notebooks in Pasteur's own hand, of which more than one hundred are laboratory notebooks recording his day-to-day scientific activities over the full sweep of his forty years in research. Until these manuscripts are deciphered, edited for publication, and subjected to critical scrutiny, our understanding of Pasteur and his work will remain incomplete. There is no prospect that this monumental task will be accomplished anytime soon, not even with the stimulus of the centenary of Pasteur's death in 1995. Indeed, the task has not even begun in any systematic way, and a full and proper edition of Pasteur's papers and manuscripts will require a massive investment of time and resources.

For the foreseeable future, we shall have to contend with a vast reservoir of unedited and unpublished manuscripts. True, Pasteur Vallery-Radot long ago published a small but significant sample of the collection, including notably a four-volume selection of Pasteur's correspondence.[4] Some of these letters, when read critically in the light of other sources, already reveal a Pasteur who was more complex and interesting than he has been seen, or indeed wished to be seen. Yet even these published letters have been surprisingly under-utilized by students of Pasteur's career. They have done little to add nuance or depth to the standard Pastorian legend. In the popular imagination, Pasteur remains the great and selfless "benefactor of humanity" who single-handedly slashed through the prejudices of his time to discover a set of scientific principles unmatched in their impact upon the daily lives and well-being of humankind.

But as the centenary of Pasteur's death approached, his oft-examined career attracted still greater attention, some of it more critical than the usual celebratory accounts. Much of the revaluation now underway has focused on Pasteur the man, whose human foibles and difficult personality have never been entirely absent from the published record but are now gaining wider publicity. But Pasteur the scientist is also being subjected to the more systematic critical scrutiny that his importance and influence deserve. That is not to suggest that Pasteur's life can be neatly divided into its scientific and nonscientific aspects. In some ways, his scientific style seems a virtual extension of his personality, and one theme of this book will be that his scientific beliefs and modus operandi were sometimes profoundly shaped by his personal concerns, including his political, philosophical, and religious instincts.

As this book unfolds, it will become clear how much the standard Pastorian legend needs to be qualified, even transformed. That point will be made most explicitly in the last chapter, "The Myth of Pasteur," which will also serve as a bibliographical essay of sorts. Long before that last chapter, however, the standard Pastorian saga will begin to unravel. For now, I want only to emphasize that the most important revelations in this book are the result of focusing on what I have chosen to call "the private science of Louis Pasteur."

PRIVATE SCIENCE AND LOUIS PASTEUR

The choice of this phrase for the very title of this book deserves a preliminary discussion and justification, if only because some readers may consider it a contradiction in terms. If, as many assume, the very definition of science implies a public (usually published) product—if, as Charles Gillispie has written, "science is nothing until reported," or if, in Gerard Piel's words, "without publication, science is dead"[5]—whatever can "private science" mean?

The notion of private science is indeed problematic, and not only in the sense that these commentators probably have in mind. Strictly speaking, there may be no such thing as purely private science or knowledge—or even a purely private thought. Even the most solitary scientist is heir to a tradition of thought, practices, techniques, training, and social experiences. Perhaps this was part of what the Victorian physicist John Tyndall had in mind when he wrote in 1885, in his introduction to the English translation of the first biography of Pasteur, that "[t]he days when angels whispered into the hearkening human ear, secrets which had no root in man's previous knowledge or experience, are gone for ever."[6] Tyndall's immediate purpose was to convey his inductivist skepticism toward the alleged role of "preconceived ideas" in Pasteur's research, but his general point can be extended to the realm of seemingly private thoughts or practices of any sort.

For, in fact, there is always a continuum between private thought or practices and public knowledge, whatever the field. The thoughts of the individual scientist alone in his or her study or laboratory will perforce be filtered not only through an inherited tradition, but also through the scientist's *anticipations* of audience response to the communication of those ideas. The scientist will always be aware that the anticipated audience may be large or small, friendly and receptive, or skeptical or hostile. According to the Russian cultural critic Mikhail Bakhtin (1895–1978), thought itself is nothing but "'inner speech,' or social conversations we have learned to perform in our heads." On this view, "when we think, we organize possible 'dialogues' with other people, whose voices and implicit social values live within us."[7] One might even say that something like a "sociology of the mind" is always at work. As we shall see in the case of Pasteur, and as the famous example

of Darwin amply reveals, this sociology of the mind can temper, modify, repress, or forever silence a "passing thought."[8]

Similarly, the "private" correspondence of a scientist (or anyone else) is obviously written with at least one recipient in mind. In the case of famous correspondents, including the mature Pasteur, some presumably private letters are clearly also being addressed to that larger audience known as "posterity." More generally, as Stephen Jay Gould has suggested, there is little reason to suppose that "private letters somehow reveal the 'real' person underneath his public veneer." This common notion, says Gould, is a "misplaced, romantic Platonism":

> People have no hidden inner essence that is more real than their overt selves. If [a scientist] reacted one way to most people in public life, and another to his sister in letters, then the public man is most of the whole. We meet a different [scientist] in these letters, not the truer core of an essential personality. These letters do not show us the real man. They simply remind us once again that people have the dammedest ability to compartmentalize their lives; one can be a fine statesman and a cad at home, a financial genius and an insensitive lout, a lover of dogs and a murderer of people.[9]

Gould's point can be extended to private documents of any sort, including even laboratory notebooks. They may provide revealing insights into a scientist and his or her work, but they do not offer uniquely privileged access to the "real" story as opposed to the public "myth." In the case at hand, Pasteur's public performances must also be incorporated into our understanding of him and his science, as with any other social actors and their work.

"Private science" becomes a still more problematic category when the research involves assistants and collaborators, as it did throughout much of Pasteur's career (and as it does in most modern laboratory research). Even Pasteur, despite his secrecy and "Olympian silence" about the direction of his research, could not always conceal his work or thoughts from his closest collaborators.[10] And a few of them did not always and forever honor Pasteur's stricture that the research carried out in his laboratory should remain a totally private affair within the Pastorian circle unless and until he chose to disclose the results himself or specifically authorized others to do so. True, Pasteur's collaborators did honor this demand to a degree that may seem astonishing in our less discreet world, and nearly all of them continued to do so even after the master's death. But there is evidence to suggest that these severe restrictions on public disclosure did not always sit well with some of Pasteur's assistants and co-workers. By 1880, for example, Emile Roux, his major collaborator in research on anthrax, rabies, and other diseases, was warning Pasteur that outsiders had begun to regard his laboratory at the Ecole Normale as a "mysterious sanctuary."[11] Eventually, the veil of secrecy was pulled back in part, most notably in the anecdotal reminiscences of Pasteur's own nephew and sometime personal research assistant, Adrien Loir, who did, however, wait half a century to publish his revelations in a widely ignored series of essays that carried the apt title, "In the Shadow of Pasteur."[12]

One could raise still other objections to the whole notion of "private science," but I will proceed as if the term embodies a meaningful distinction. Throughout this book, I will use the term "private science" in the informal sense of those scientific activities, techniques, practices, and thoughts that take place more or less "behind the scenes." That definition might be less appropriate in the case of a scientist whose activities and career were less theatrical than Pasteur's, but his carefully orchestrated public performances invite a close examination of the private dress rehearsals. Finally, I should stress that my notion of "behind the scenes" is not restricted to activities and thoughts that were literally kept out of public view, but will occasionally be extended to matters that can be found in the published record if one looks hard enough, but have been lost from that collective public memory represented by the standard Pastorian legend.

This approach means, among other things, that I will sometimes highlight relatively obscure features of Pasteur's published papers or correspondence, and will pay much closer attention than usual to some of the supporting cast, including a few of the once public but now mostly forgotten critics of the star. Nonetheless, the most striking revelations come when one brings to center stage some of the activities and ideas recorded only in Pasteur's unpublished manuscripts. This book makes selective use of the full range of the manuscript materials that Pasteur left behind. In the most dramatic cases, however—including Pasteur's crowning work on vaccines against anthrax and rabies—the crucial evidence will come from his laboratory notebooks. It is therefore worth saying something now about my attitude toward these very special documents.

PASTEUR AND HIS LABORATORY NOTEBOOKS

The most private of the manuscript materials Pasteur left behind are the 144 holographic notebooks that his grandson donated to the Bibliothèque Nationale in 1964. Of these 144 notebooks, 42 fall outside the category of laboratory notebooks, consisting instead of collections of newspaper clippings, draft sketches of projected books that never appeared, lecture outlines, and reading and lecture notes. The remaining 102 notebooks represent the most precious documents in the Papiers Pasteur. They consist of

careful and detailed records of experiments carried out by Pasteur and his collaborators during forty years of active, almost daily research. They are the central repository for the private science of Louis Pasteur, the documents he once asked his family to keep forever out of public view. During his lifetime, he carefully guarded them from others, including his closest collaborators. Even when he left Paris for trips or holidays, Pasteur took the most current of the laboratory notebooks with him. His co-workers sometimes experienced inconvenience or worse because of his insistence on total control of the notebooks.

In late November 1886, for example, while Pasteur was resting at a villa on the Italian Riviera for the sake of his fading health, his collaborators in Paris were suddenly faced with a legal problem connected with the death of a boy who had undergone the Pastorian rabies treatment (a story to which we shall return in Chapter Nine). As we know from his retrospective personal testimony, Pasteur's nephew-assistant Adrien Loir had to be dispatched quickly to Italy in order to retrieve important details about the boy's treatment—information that was recorded only in a laboratory notebook the master had taken with him to the Italian villa.[13] Earlier, in July 1883, when Emile Roux wanted to gather together some of the results of his important work on rabies for his doctoral thesis, he had to seek Pasteur's permission to use information recorded in the laboratory notebooks. To ensure the master's assent, Roux promised to expose only those results already made known in a general way in Pasteur's published papers, submitted a draft version to the master for his corrections and revisions, and "inscribed your [i.e., Pasteur's] name on the first page of this exposition of studies that belong to you."[14]

In 1896, a year after Pasteur's death, Roux gave a revealing, if surprisingly restrained, account of the master's proprietary attitude toward his laboratory notebooks. Roux's account also deserves attention because it reveals the extent to which the work in Pasteur's laboratory had become a collaborative affair by the time Roux participated in it:

> In order to be nearer the work, master and disciples lived in l'Ecole Normale. Pasteur was always the first to arrive; every morning, at 8 o'clock, I heard his hasty step . . . over the loose pavement in front of the room which I occupied at the extremity of the laboratory. As soon as he had entered, a bit of paper and pencil in his hand, he went to the thermostat to take note of the state of the [microbial] cultures and descended to the basement to see the experimental animals. Then we made autopsies, cultures and the microscopic examinations. . . . Then Pasteur wrote out what had just been observed. He left to no one the care of keeping the experimental records; he set down most of the data which we gave him in all its details. How many pages he has thus covered, with his little irregular, close-pressed handwriting, with drawings on the margin and references, all mixed up, difficult to read for those not accustomed to it, but kept nevertheless with extreme care! Nothing was set down which had not been established; once things were written, they became for Pasteur incontestable verities. When in our discussions, this argument resounded, "It is in the record book," none of us dared to reply. The notes being taken, we agreed upon the experiments to be made; Pasteur stood at his desk ready to write what should be decided upon. . . .
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> Then we spent the afternoon in making the experiments agreed upon. . . . Pasteur returned toward five o'clock. He informed himself immediately of all that had been done and took notes; his notebook in hand, he went to verify the tickets fastened on the cages, then he told us of the interesting communications heard at the [Académie des sciences earlier in the afternoon] and talked of the experiments in progress.[15]

As Roux reports, Pasteur did indeed keep a detailed and meticulous record of the experiments carried out in his laboratory. I have never counted the pages that Pasteur filled with experimental data in his sometimes crabbed and microscopic hand, but they probably exceed ten thousand. As some of the illustrations in this book suggest, the task of deciphering and interpreting Pasteur's entries is often daunting. Like most laboratory notebooks, Pasteur's usually consist of bare records of experiments, with only occasional hints as to their aim or theoretical significance. The meaning of such documents cannot begin to be grasped without an intimate familiarity with the scientist's published work. Beyond that, their would-be interpreter should ideally possess a combination of skills akin to those of the paleographer, cryptographer, and mind-reader. It is a species of detective work in which tantalizing clues too often lead to dead ends.

But the effort is exhilarating as well as exhausting. Words cannot fully convey the sense of excitement that comes from turning the pages of any one of Pasteur's laboratory notebooks. It is as if one were looking over his shoulder as he designed and carried out experiments ranging from the trivial to the profound. The laboratory notebooks form a virtually unbroken chain of documents that record Pasteur's day-to-day dialogue with a sometimes recalcitrant nature. They are, I think, the most revealing of all the manuscript materials he left behind. Perhaps that is to be expected, since Pasteur did after all spend most of his waking hours at work in the laboratory.

To produce a detailed account of all of Pasteur's one hundred laboratory notebooks, several decades of work will surely be required. I have therefore focused attention instead on a few episodes in Pasteur's career where there are distinct—and sometimes astonishing—discrepancies between the

results reported in his published papers and those recorded in his private manuscripts. This approach is open to several objections. It is one thing to be selective in order to reduce the task to manageable limits. But why choose such special and possibly misleading criteria? If most of Pasteur's published accounts are consonant with his laboratory records, why focus on the exceptions? Can such an approach give us a balanced assessment of Pasteur's usual scientific practice? Will not the full range of his achievement be lost through such an episodic treatment of his career? And is this not an especially suspect approach at a time when so much public attention is being drawn to a few spectacular examples of real or alleged fraud in science?[16] Is even Pasteur to be swept up in the current fashion for muckraking exposés of science and its legendary heroes?

Only as this book unfolds can the reader begin to judge whether or how far these objections have been met. But it may be useful to address them in a preliminary way even now. In doing so, I will be able to clarify my aims and to insist on some of the virtues of my approach. Let me emphasize at once that I have no intention of denying Pasteur's greatness as a scientist. To be sure, my definition or conception of a "great scientist" may differ somewhat from the conventional. For me, there is no reason to suppose that a great scientist must also display personal humility, selfless behavior, ethical superiority, or political and religious neutrality. The historical record often enough reveals the opposite. For me, past scientists are not great insofar as they were the "first" to advance concepts that look "right" in the light of current knowledge, nor insofar as they adhered to the precepts of an allegedly clear-cut Scientific Method that their lessers and rivals presumably violated. For me, rather, past scientists are great insofar as they persuaded their peers to adopt their ideas and techniques and insofar as those ideas and techniques were fertile in the investigation and resolution of important research problems. Pasteur was no exemplar of modesty, selflessness, ethically superior conduct, or political and religious neutrality. Nor was he always "first," "right," or a rigorous practitioner of the Scientific Method as usually conceived. But he was a remarkably effective and persuasive advocate for his views, and his concepts and techniques were immensely fertile in the pursuit of a wide range of important scientific and technical problems. By these criteria, he deserves his reputation as one of the greatest scientists who ever lived.

But let me turn, at greater length, to the more specific objection that it is misleading and unfair to adopt an episodic approach that emphasizes the "exceptional" discrepancies between Pasteur's published writings and his "private science." To begin with, the episodes on which I focus are far from trivial: each concerns a major phase or turning point in Pasteur's research.

Nor are they concentrated in any narrow field or period of his career. They span his active career and concern fields as varied as crystallography, molecular asymmetry, fermentation, spontaneous generation, vaccination and immunization, and veterinary and human medicine. The three episodes examined most closely here through the use of Pasteur's laboratory notebooks concern his first great discovery (of optical isomers in the tartrates), his most famous public experiment (the anthrax vaccination experiment at Pouilly-le-Fort), and his most famous achievement of all (the application of a rabies vaccine to human subjects). With the admittedly significant exception of his investigation of the silkworm diseases, the only major topics of Pasteur's research that receive no focused attention here are his conceptually undistinguished studies on the manufacture and preservation of vinegar, wine, and beer.

Nor is it likely that the discrepancies on which I focus are really exceptional. My sample is far from complete. Many additional examples will surely emerge as the entire corpus of Pasteur's notebooks is subjected to systematic analysis. On the other hand, it is crucial to emphasize that the discrepancies between Pasteur's public and private science do fall into two very different categories of very different significance.

LABORATORY NOTEBOOKS, SCIENTIFIC FRAUD, AND THE RHETORICAL CONSTRUCTION OF SCIENTIFIC KNOWLEDGE

Most of the discrepancies between Pasteur's public and private science are of a sort that will come as no great surprise to working scientists, or to anyone who has been attentive to recent historical scholarship on laboratory notebooks. To these audiences, it will be obvious that such discrepancies are part and parcel of the process by which "raw data" are transformed into published "results." In the interests of brevity, clarity, logical coherence, and rhetorical power, the published record always projects a more or less distorted image of what the scientist "really" did.

For some reason, laboratory notebooks were long overlooked by historians of science, but their virtues as a strategic site of inquiry have become evident in recent years. The recognition of their special value owes much to the pioneering work of M. D. Grmek and F. L. Holmes, both of whom used the laboratory notebooks of Pasteur's friend and contemporary, the great French physiologist Claude Bernard (1813–1878), to produce two brilliant and complementary books published twenty years ago. Grmek's book of 1973 focused on Bernard's work on poisons (notably curare and carbon

monoxide), while Holmes's book of 1974 gave an exhaustive account of Bernard's early research in digestive physiology.[17] In the wake of these path-breaking works, other valuable analyses of laboratory notebooks have already appeared—two striking examples being David Gooding's work on the notebooks of Michael Faraday (1791–1867) and Gerald Holton's investigation of the laboratory notes of the American Nobel laureate in physics, Robert Millikan (1868–1953).[18] But it is Holmes who has become the leading advocate and practitioner of the study of laboratory notebooks. In the years since his book on Bernard, Holmes has produced comparably detailed and insightful analyses of the laboratory notebooks of the great eighteenth-century French chemist Antoine Lavoisier (1746–1794) and Nobel laureate biochemist Hans Krebs (1900–1981) of "Krebs Cycle" fame.[19] We can surely expect other significant studies of this sort as historians uncover more examples of scientists who have earned our gratitude by preserving these traces of their daily work in the very special literary genre known as the laboratory notebook.

Much remains to be done in this line of research. But in every case thus far in which records of "private science" have been closely investigated, one can detect discrepancies of one sort or another between these records and published accounts. Even the best scientists routinely dismiss uncongenial data as aberrations, arising from "bad runs," and therefore omit or "suppress" them from the published record. Equivocal experiments are sometimes transformed into decisive results. The order in which experiments were performed is sometimes reversed. And the actual nature or direction of research is otherwise simplified, telescoped, and generally "tidied up." There is rarely anything sinister about such practices, rarely any intention to deceive, and their existence has long been recognized. As long ago as the seventeenth century, Francis Bacon noted that "never any knowledge was delivered in the same order it was invented," while Leibniz expressed his wish that "authors would give us the history of their discoveries and the steps by which they have arrived at them."[20] From time to time ever since, scientists and others, including the influential American sociologist of science Robert K. Merton, have drawn renewed attention to this "failure of the public record to record the actual course of scientific inquiry."[21]

More recently, analysts of the scientific enterprise have moved from expressions of regret about the discrepancies between private and public science to a recognition of their rhetorical import in the construction of scientific knowledge through the literary genre of the scientific paper. In the case of Millikan, for example, Holton shows us a country bumpkin from rural Illinois who was initially so naive about the genre that he included *all* of his experimental data about the quantity of charge on the electron, supporting

his view of its unitary charge by publicly assigning more or fewer "stars" to what he considered good or bad runs. Millikan was quickly enlightened by his experience and the advice of others; never again did he resort to public displays of his less persuasive data. And Holton insists that Millikan's later published papers can actually be seen as "better" (i.e., more persuasive) science than that represented in his first paper, with its needlessly candid full disclosures.[22]

More recently still, Holmes has extended his approach beyond the analysis of laboratory notebooks to ask broader questions about the history of the practice of laboratory record keeping and its relation to the published record of science. In the case of Lavoisier, Holmes has shown the extent to which a scientist's ideas can be altered in the very process of "writing up" the results from laboratory notebooks for publication, and in the case of Krebs he has had the rare opportunity of comparing his historical reconstructions of events from laboratory notebooks with Krebs's own recollections of his investigative trail. In neither of these cases, nor in the case of Bernard, does Holmes suggest that his historical actors engaged in deliberately deceptive practices. Instead, he maintains that Lavoisier, Bernard, and Krebs simply and wisely adopted the standard practices and rhetorical strategies that always intervene between private laboratory records and their effective and persuasive presentation in the public domain.[23]

Against this background, it should be clear that Pasteur was not committing "scientific fraud" whenever his laboratory notebooks reveal a course of research different from that recorded in his published works. Long before his day, and perhaps especially in France, the institutionalization of the scientific paper—its progressive codification into a formulaic literary genre—had reached a point that discouraged instructive disclosures of the sort Bacon and Leibniz once thought might emerge from a closer fit between private research and its public presentation.[24] On Holmes's account, the institutionalized scientific paper did not (and does not) deliberately "suppress" uncongenial private data, but rather seeks to provide an efficient and authoritative public presentation of the most pertinent results to an expert audience with little need of elaborate additional detail.[25] By Pasteur's day, a pattern of formulaic discrepancies between public and private science was already long-standing and widespread, if not overtly sanctioned.

But the existence of this practice does not make such discrepancies insignificant or uninteresting, in Pasteur's case or any other. Precisely because they were and are so common, these formulaic discrepancies deserve much closer attention. To ignore or trivialize them is to miss the force of Peter Medawar's now-hackneyed warning that "scientific 'papers' [do] not merely conceal but actively misrepresent the reasoning that goes into the work they

describe."[26] As Medawar suggests, to rely solely on the published record is to distort our understanding and appreciation of science as it actually gets done. The effect is impoverishing in several respects. By making the results of scientific inquiry look more decisive and straightforward than they really are, the published record tends to conceal the pliability of nature. It eviscerates science of its most creative features by conveying the impression that imagination, passion, and artistry have no place in scientific research. It makes it seem as if scientific achievement and innovation result not from the impassioned activity of committed hands and minds, but rather from passive acquiescence in the sterile precepts of the so-called Scientific Method. More specifically, as Medawar emphasizes, the published record tacitly endorses a naive and long-outmoded "inductivist" or "empiricist" philosophy of science, according to which scientific truth emerges from the innocent and unprejudiced observation of raw facts. The superficially objective and dispassionate image of science thus conveyed is bought at the price of much of its zest and human appeal. The construction of scientific knowledge is a much more interesting process than its published record suggests.

There are, of course, those who insist that "genuine" scientific knowledge is independent of the process by which any particular scientist arrives at his or her conclusions. In very different ways, philosophers and sociologists of science tend to be suspicious of historical studies of individual "scientific creativity." For philosophers in the tradition of Karl Popper, such studies seem to be pursuing a will-o'-the-wisp, an elusive "psychology of discovery," at the expense of a clear-cut "logic of justification." For them, the object of study is the published text, and the "scientificity" of a given text is to be assessed in terms of logical and methodological criteria that transcend particular individuals, particular social groups, or any contingent historical circumstances.

For sociologists of knowledge, by contrast, studies of individual scientific activity run the risk of ignoring the extent to which scientific knowledge is a community affair—the outcome of a complex process of social negotiation. On this view, scientific knowledge is constructed within a culturally limited space. For some, the boundaries of that space are set by the broadly cultural "interests" of participants. More recently, attention seems to have shifted to more sharply localized, "internal" material and technical constraints—a trend that may invite the risk (or opportunity) of a return to positivist or inductivist epistemologies.

Often lost from sight in such theoretical discussions is the real individual scientist who tries to navigate a safe passage between the constraints of empirical evidence on the one hand and personal or social interests on the

other. To chart such individual passages is certainly to leave aside some important general issues about the nature and construction of scientific knowledge. Yet there remains a place for studies of individual scientists and their creative activity. To proceed as if scientific knowledge were somehow achieved all apart from the activity of individual scientists is itself a distortion of reality. For the historian, one way to reduce such distortions is to explore the process of scientific research as recorded day to day in surviving laboratory notebooks.

That is not to say—to repeat a point already made—that these private documents somehow permit direct access to the "real" work of the scientist. Even laboratory notebooks are incomplete *traces* of activity, much of which remains tacit, none of which can be observed directly, and all of which must be deduced from recorded inscriptions that are often difficult to decipher and interpret. Sociologists and anthropologists of knowledge have the advantage of being able to interview and observe participants *in the very process* of doing science, and some important results have already emerged from recent research along these lines. Responding—sometimes explicitly—to Medawar's challenge to subject science to "an ethological enquiry," to study what scientists actually *do* by "listening at the keyhole," some sociologists and anthropologists of science, notably Harry Collins and Bruno Latour, have uncovered important elements of what is variously called the "private," "personal," "tacit," or "craft" knowledge that is fundamental to the actual practice of science but finds few echoes in the published literature—or, for that matter, in unpublished laboratory notebooks. These sociologists or anthropologists can watch the scientist go about his or her "craftsman's work" and thus observe the nonverbal activity that accompanies and gives rise to verbal and other symbolic accounts. In short, they can go much further toward recovering the actual *activity* of science before it becomes encoded in fading and incomplete verbal or graphic "inscriptions," including laboratory notebooks.[27]

But if historians lack these advantages, they can be relatively sure that the episodes they choose to study are already known to be of special interest. Anthropologists of science may hang around a laboratory for a year or more and witness no obvious peaks of productivity. Historians, by contrast, can be selective in their choice of notebooks, which nonetheless bring them closer in time and place to the creative work of scientists than do any published results. At a minimum, laboratory notebooks give the historian another set of "texts" to read, and the work of Grmek, Holmes, Holton, and others has already provided ample evidence that a comparison of these "private" texts with the published literature can yield important insights of general significance.

In the spectacular case of Pasteur, we are fortunate to have a complete set of his unpublished laboratory notebooks—those one-hundred-odd tidy and meticulously preserved records of his day-to-day research. By exploring his laboratory notebooks in the full context of his life, work, and social setting, we can gain unusual insight into the construction of scientific knowledge at the concrete level of an extraordinarily creative individual scientist.

This book can only begin the task, and for the most part these more general concerns will only emerge implicitly. Yet it should gradually become clear that some of Pasteur's most important work often failed to conform to ordinary notions of proper Scientific Method. In particular, it will become clear that Pasteur sometimes clung tenaciously to "preconceived ideas" even in the face of powerful evidence against them. And it should also eventually become clear just how far the direction of his research and his published accounts of it were shaped by personal ambition and political and religious concerns. We will become aware of his ingenious capacity for producing empirical evidence in support of positions he held a priori. In other words, one aim of this book is to show the extent to which nature can be rendered pliable in the hands of a scientist of Pasteur's skill, artistry, and ingenuity. But it will also suggest that not even Pasteur's prodigious talent always sufficed to twist the lion's tail in the direction he sought. Nature is open to a rich diversity of interpretations, but it will not yield to all.

PASTEUR AND THE ETHICS OF BIOMEDICAL RESEARCH

These themes and issues continue to appear in the second part of the book, which concerns episodes in Pasteur's veterinary and biomedical research. But now an additional focus begins to take center stage, and it relates directly to the second and very different category of discrepancies between Pasteur's public and private science. Here we deal not with mere acquiescence in the formulaic genre of scientific papers and the associated "inductivist" image of science, but with discrepancies between Pasteur's public and private science in cases where the word "deception" no longer seems so inappropriate, and even "fraud" does not seem entirely out of line in the case of one or two major episodes. These are serious allegations, and they will be treated with the care they deserve.

Only a very few episodes are in question here, and two of them are so close in time and so similar in nature that it is better to conflate them into one. Moreover, as we shall see, this "double episode" is relatively easy to explain and excuse, since it concerns "therapeutic experiments" on seemingly doomed victims of rabies and is at worst an example of deception by

omission. Instead of informing the public and the scientific community of the dramatic results of these two human trials, Pasteur chose to remain completely silent.

The other episodes concern the two most celebrated achievements in Pasteur's career: his bold public demonstration of a vaccine against anthrax in sheep at Pouilly-le-Fort in 1881, and the first known application of his rabies vaccine to a human subject, young Joseph Meister, in July 1885. In the first case, as we shall see, Pasteur deliberately deceived the public and the scientific community about the nature of the vaccine used in the experiments at Pouilly-le-Fort. In the second case, the nature of Pasteur's deception is less clear-cut, but here too we will find some striking discrepancies between the public and private versions of the famous story of Joseph Meister.

Let it be clear at the outset that I am less concerned to *expose* Pasteur's public deceptions than to *explain* them. True, the ascription of motives to historical actors is a notoriously risky business, and this is very definitely the case here. In every case, it is possible to offer exculpatory explanations for Pasteur's behavior—though credulity is sometimes strained, especially in the case of the sheep-vaccination experiments at Pouilly-le-Fort and certain aspects of his work on rabies. But the effort to analyze Pasteur's ethically dubious deceptions is justified by the importance of the larger questions these few episodes raise. In what circumstances, and under what pressures, is a scientist of Pasteur's stature tempted to deceive? To what extent is such conduct explicable in terms of personal circumstances or character, and to what extent in terms of a competitive ethos or other more general cultural forces? Are the presumed norms of scientific conduct always reconcilable? Do scientific advance and the public welfare sometimes require scientists to tell "white lies"? How can the public or even other scientists be expected to appreciate the intuitive basis for actions that cannot be fully justified in strictly "scientific" terms? Is there a difference between "scientific ethics" and "medical ethics"? Especially in the face of dread disease and terrified people, how much prior evidence from animal experiments is required before preventive measures are applied to human cases? At least implicitly, Pasteur's deceptions raise these and other equally important questions about the ethics of research in general and of biomedical research in particular.

But in the midst of these absorbing and more or less timeless issues, it should not be forgotten that our subject is a particular individual in a specific historical context. We must not wrench Pasteur from his historical circumstances for the sake of facile insights into our current concerns. There are profound differences between the intellectual, social, and ethical

climate of his day and our own. His ethical conduct, like his scientific achievements and practices, should and will be assessed by applying criteria and standards that were recognized by his contemporaries and, indeed, by Pasteur himself.

WHAT DO WE DO WHEN PRIVATE SCIENCE BECOMES PUBLIC KNOWLEDGE?

At this point, it will prove useful to circle back to the beginning of this chapter and to disclose the context in which Pasteur instructed his family to keep his laboratory notebooks forever out of the public eye. Pasteur did not fear the exposure of some deep and dark secret recorded only in his notebooks. Instead, his directive was a plausible response to a specific wrenching experience he had just gone through.

In February 1878, Pasteur mourned the death of his friend and compatriot, the great experimental physiologist Claude Bernard. About six months later, one of Bernard's disciples instigated the publication of some fragmentary laboratory notes he had left behind. The contents of Bernard's hitherto private notes surprised Pasteur and their publication placed him in an awkward position. In essence, these private notes disputed Pasteur's "germ theory" of fermentation. While alive, Bernard had never challenged that theory in public nor even in conversation with Pasteur. Pasteur felt obliged to respond to these now public manuscript notes, lest his deeply held theory of fermentation be undermined by appeal to the authority of the revered Bernard. If he felt uncomfortable about attacking the private work of his late friend and frequent public supporter, who could no longer disavow or defend the experiments in question, Pasteur did nonetheless publish a full-length critique of Bernard's manuscript notes. By carefully repeating Bernard's experiments and comparing them with his own, Pasteur went a long way toward establishing his claim that Bernard's results were mistaken, dubious, or misinterpreted. Both in tone and substance, the critique was devastating.[28]

Pasteur's conduct in this affair was by no means universally approved. Half a century later, Paul de Kruif, whose best-selling book *The Microbe Hunters* did so much to popularize Pasteur's work in the United States, fulminated against Pasteur's behavior in this case. For de Kruif, Pasteur's conduct when faced with the publication of Bernard's private notes served as the most striking example of his inability to accept criticism of any sort. Worse yet, it displayed Pasteur's willingness to stomp on the grave of

a revered and recently deceased colleague solely for the sake of his own reputation.[29]

Pasteur was himself concerned that this tirade against Bernard would be unpopular among important segments of the French scientific community and larger public. To justify his assault against the work of one of France's scientific heroes, Pasteur adopted a two-pronged strategy. On the one hand, he impugned the motives of the man who had arranged for the publication of Bernard's private notes, the distinguished French chemist Marcellin Berthelot (1827–1907), a long-standing advocate of a modified "chemical" theory of fermentation as opposed to Pasteur's strictly 'biological" theory. Pasteur accused Berthelot of misusing and debasing Bernard's reputation by publishing these crude preliminary experiments. If his critique tarnished Bernard's memory, Pasteur insisted, then Berthelot must accept much of the responsibility. For it was he who had tried to bolster his own misguided and doomed campaign against the germ theory of fermentation by bringing unauthorized public attention to bear on Bernard's private and preliminary experiments on fermentation.[30]

But Pasteur also justified his critique on methodological grounds. For him, Bernard's manuscript notes represented an instructive example of the danger of "systems" and "preconceived ideas." Bernard himself had done much to expose this danger in his famous *Introduction to the Study of Experimental Medicine* (1865), a masterful discussion of Scientific Method by one of its leading practitioners. Yet somehow, Pasteur insisted, Bernard had forgotten his own wise precepts in these private notes on fermentation. Bernard had been led astray, Pasteur continued, by his a priori conviction of a fundamental opposition between organic syntheses and organic decompositions. He supposed that organic syntheses were peculiarly vital phenomena, while organic decompositions—including fermentation, combustion, and putrefaction—were physicochemical rather than vital processes. For Bernard, in effect, organic syntheses were associated with life, while fermentation and other organic decompositions were associated with death. Because Pasteur's theory linked fermentation with life, Bernard privately rejected it and undertook experiments in hopes of refuting it. In Pasteur's eyes, Bernard was secretly opposed to the biological or germ theory of fermentation because it clashed with his general conception of organic processes—with his "system" of "preconceived ideas" about such phenomena.[31]

It is less important here to assess the validity of Pasteur's charges against Berthelot and Bernard than to recall that they arose in response to the posthumous and unauthorized publication of Bernard's laboratory notes. For it was also in response to this event that Pasteur instructed his family to

protect the privacy of his own notebooks.[32] He clearly feared that the publication of some of his laboratory notes might do similar damage to his reputation. At that point, he was presumably concerned only about his reputation for experimental probity and methodological propriety, for none of the ethically dubious episodes discussed in this book had yet occurred.

Pasteur criticized Bernard's posthumously published notes in large part to defend his own theory of fermentation. But he also seized the opportunity to draw methodological lessons from Bernard's once-private laboratory notes. In doing so, Pasteur supplied an inadvertent precedent and justification for exposing his own manuscripts to critical scrutiny. And the results, as we shall see, bear no resemblance to the lesson that Pasteur professed to find in Bernard's manuscript notes.

In presenting Bernard's private experiments as an example of the "tyranny of preconceived ideas," Pasteur wrote as if he were surprised to discover that a scientist of Bernard's stature and methodological self-consciousness could sometimes stray from the path of objectivity. He expressed dismay that even Bernard could sometimes be seduced by that "greatest derangement of the mind . . . believing things because one wants to believe them."[33] In the context of this polemic, Pasteur presented himself as a practitioner of the "inductive scientific method, working outside of theories."[34] Yet elsewhere he spoke of the fertility of his own "preconceived ideas,"[35] and he sometimes seemed to advocate something like the hypothetico-deductive method now favored by many philosophers of science.

In truth, Pasteur did not think very deeply about questions of Scientific Method, and he presented conflicting accounts of his own methodology depending on the audience and purpose at hand. To understand and appreciate Pasteur's scientific modus operandi, it is essential to examine what he actually did in his laboratory rather than to read his scattered and inconsistent remarks about Scientific Method. The crucial source for penetrating the ways in which Pasteur produced scientific knowledge is the extensive set of laboratory notebooks he left behind. Unlike Bernard's notebooks, moreover, Pasteur's manuscripts also bring us face-to-face with important questions about the ethics of biomedical research. To that extent, we may hope to learn even more from them.

Given Pasteur's concern about exposing his laboratory notebooks to public scrutiny, it may seem surprising that they survived him at all, let alone that he should have preserved them so meticulously. Perhaps his concern passed with time, but there is no reason to suppose that he would have welcomed the prospect of a future inquiry of the sort embodied in this book or other recent scholarship. It may be doubted, in short, that Pasteur saved his laboratory notebooks with future historians in mind. True, he did profess great interest in the history of science, even suggesting that it should be taught as part of the regular science curriculum at the Ecole Normale Supérieure.[36] He often sprinkled his memoirs and lectures with historical allusions and wrote a substantial historical article on the life and work of Lavoisier.[37] As a working scientist, however, Pasteur valued the history of science only insofar as he thought it could advance the cause of science and scientists. He held a heroic conception of the history of science according to which great men bring us ever closer to absolute truths about nature. And when he proposed that the history of science be incorporated into the science curriculum at the Ecole Normale, he did so in the belief that it might inspire students to respect and honor their elders and forebears by revealing how difficult it was to produce original scientific work.[38]

If Pasteur believed that a future study of his own laboratory notebooks or other manuscripts might contribute toward these or other worthy goals, he did not say so. The pains he took to preserve his notebooks can almost surely be traced instead to two very different considerations: (1) he repeatedly returned to his records of old experiments to inspire or test new ideas, and in that sense his laboratory notebooks were of direct and continuing utility to him; and (2) like a pack rat, he saved absolutely *everything* anyway, as many an archivist would attest after trying to make sense of the mounds of isolated and sometimes trivial slips of paper he left behind.

We are, in any case, fortunate that Pasteur left us these detailed records of his ongoing research. Indeed, one's sense of gratitude is so great that one might feel almost churlish about using them in any way that their author did not intend or foresee. But Pasteur's notebooks are now public property, available to anyone who gains access to the manuscript room of the Bibliothèque Nationale in Paris. In an important sense, it is no longer possible to invade Pasteur's privacy, for his "private science" has now become part of the public domain. We are thus, in some ways, placed in a situation like the one facing Pasteur upon the publication of Bernard's laboratory notes on fermentation. And it is precisely for that reason that we can insist that the standard Pastorian legend requires revision and even transformation. As the contents of these once private documents find their way into public view, a fuller, deeper, and quite different version of the Pasteur story will perforce emerge. There is, in effect, a new "history of Pasteur" to be written.

science, and the newspapers have lately been filled with examples of the fraud that can result when the norm of truth-telling is overwhelmed by the quest for personal status and recognition.[96] In truth, however, Pasteur's deception at Pouilly-le-Fort cannot properly be compared with the more egregious (if still rare) examples of recent "scientific fraud." We do not have to do here with any outright fabrication of data. And if Pasteur did almost everything he could to convey the impression that the vaccine used at Pouilly-le-Fort had been prepared by "his" method of oxygen-attenuation, he did not quite go so far as flatly to lie: he never did say, in so many words, "the vaccine used at Pouilly-le-Fort was an oxygen-attenuated vaccine."

More than that, Pasteur was surely motivated in part by a well-founded concern that a full disclosure of the events at Pouilly-le-Fort would lead his more hostile critics to award Toussaint credit for the discovery of vaccination against anthrax, despite the very real technical differences between their procedures and results. That this concern was well founded is clear from the behavior of Pasteur's leading German rival, Robert Koch, who eventually hailed Toussaint as the worthy inventor of vaccination against anthrax, while persistently denigrating Pasteur's contributions to this and other branches of the new science of bacteriology or microbiology.[97] As this episode suggests, Pasteur knew his enemies well. In the end, it is mainly a measure of the importance attached to originality in modern science—and of the competitive environment in which Pasteur lived, moved, and had his being—that a significant and undeniable element of deception should have entered into the most celebrated public experiment by one of the greatest heroes in the history of science.

SEVEN

From Boyhood Encounter to "Private Patients": Pasteur and Rabies before the Vaccine

ON 18 OCTOBER 1831 a lone but menacing wolf left its natural habitat in the wooded foothills of the Jura mountains in eastern France and descended upon several nearby communities, attacking and biting everything in its path. The focus of its rampage was the village of Villers-Farlay, where eight of its human victims eventually died of rabies, but it also bit several people in and around the town of Arbois. Some of these terrified victims made their reluctant way to a blacksmith's shop in Arbois, there to submit to the traditional treatment for a rabid animal bite: cauterization with a red-hot iron—in effect, to have their wounds "branded." From a spot within earshot of the screaming victims, an eight-year-old neighborhood boy watched this scene in horror. That boy, the son of a local tanner, was Louis Pasteur.[1]

Half a century later, on 17 October 1885, the now famous Pasteur received a letter from the mayor of Villers-Farlay, one M. Perrot, who informed him that this village so near his home town had once again been the site of an attack by a rabid animal. This time there was only one victim, a fifteen-year-old shepherd named Jean-Baptiste Jupille, who had come forth to do battle with a rabid dog when it charged him and a half-dozen younger shepherds watching over their sheep in a meadow. Jean-Baptiste saved his comrades by killing the dog, but during the struggle was severely bitten on the hands. Like most well-informed Frenchmen, Mayor Perrot knew that Pasteur had been working on a vaccine against rabies and therefore sought his advice and help in the case of young Jupille. As we shall see more fully in the next chapter, Pasteur quickly agreed to undertake the treatment of this brave shepherd boy, who escaped the rabies to which he had once seemed doomed. For now, however, the point is that Mayor Perrot's letter

reminded Pasteur of the scene he had witnessed at the blacksmith's shop in Arbois half a century ago.

In fact, Pasteur's memory of his boyhood encounter with rabies remained so vivid that he asked Mayor Perrot to conduct an inquiry into this episode from the distant past. The stated aim of the inquiry was to investigate Pasteur's suspicion that those who had died of rabies after the wolf's attack of 1831 had been bitten on their hands or face, while those whose bites were confined to clothed areas of their bodies had escaped the disease. At Pasteur's request, Mayor Perrot dutifully interviewed surviving villagers who could still recall something of that terrifying day. His interviews not only confirmed Pasteur's suspicion but also provided a riveting account of the events of 18 October 1831 that is now deposited in the Pasteur papers at the Bibliothèque Nationale in Paris.[2]

Pasteur's boyhood encounter with rabies almost surely accounts for part of his later fascination with the disease. True, he made no such explicit claim himself and sometimes offered more prosaic reasons for choosing rabies as the target of his search for the world's first laboratory vaccine against a human disease. After he had achieved that goal, and as the still famous Institut Pasteur in Paris was being built with the grateful donations that this achievement inspired, he insisted in private correspondence that he had undertaken the study of rabies "only with the thought of forcing the attention of physicians on these new doctrines"—that is to say, his still controversial germ theory of disease and the technique of vaccination through attenuated cultures.[3] At an earlier point, in August 1884, when his rabies vaccine had not yet been applied to human cases, Pasteur offered a more specific reason for his interest in the disease in an address to the International Medical Congress in Copenhagen. His prior success at producing vaccines against animal diseases—chicken cholera, anthrax, and swine fever—naturally aroused hope that vaccination could be extended to human diseases. But blocking that goal was one immense obstacle—namely, that "experimentation, while allowable on animals, is criminal on man." For this reason, vaccination could be extended to man only on the basis of a deep knowledge of animal diseases, "in particular those that afflict animals in common with man."[4] As the oldest and most striking example of a lethal disease common to man and animals, rabies held special promise in the quest to extend vaccination to human diseases.

True enough, but the rabid wolf attack of 1831 also left Pasteur with a very personal and unforgettable appreciation of the popular horror of the disease. This popular horror of rabies had no basis in its statistical or demographic significance. For rabies has always been rare in man. It probably never claimed even a hundred victims in any year in France, and French

estimates for the decade just before Pasteur produced his famous vaccine indicate an annual mortality of considerably fewer than fifty.[5] Rabies was equally rare in England, where the annual mortality rate ranged from a low of one person in 1862 to a high of seventy-nine in 1877, "by far the worst year on record."[6] But despite its rarity, rabies has always held a very special place in the popular imagination. It was—until AIDS—the very model of a mysterious and horrific disease. Its usual carrier is man's best friend. Its human victims are all too often children. Its microscopic anatomical lesions and its proximate agent, a tiny filterable virus, long escaped detection and isolation, leading a few to insist that rabies could arise "spontaneously," in the absence of a rabid animal bite. One persistent theory held that the disease could result from the nervous trauma allegedly suffered by sexually frustrated dogs, and men in the throes of symptomatic rabies were sometimes said to be priapic and sexually insatiable.[7] In this and other ways, rabies became linked in the popular imagination with "animal" sexuality, bestiality, and other cultural anxieties, so much so that the appearance of rabies in a community sometimes led to panic and even to "Great Dog Massacres" that were designed to exorcise the evil disease.[8]

The terrifying spectre of "spontaneous" rabies found some, if not much, empirical sanction in the prolonged and variable interval between the bite of a rabid animal and the outbreak of symptoms in its victims. Most students of rabies had long since agreed that it was caused by a poison (or "virus") transmitted in the saliva of the attacking animal, but they had to admit that this alleged virus eluded detection and that its lethal work remained long invisible and intangible. The "incubation period" of rabies varies widely from species to species and from individual to individual. In dogs, the average is perhaps a month. In humans, the incubation period is usually a month or two, but occasionally reaches a year or more. This feature of rabies aroused profound dread in any victim of an animal bite, who could never be sure that the disease might not yet manifest itself in him or her.[9]

But it was of course the symptoms and outcome of rabies that inspired this dread. In the scarcely exaggerated popular image of the disease, rabies embodied the ultimate in agony and degradation, stripping its victims of their sanity and reducing them to quivering, convulsive shadows of their former selves. The rabies virus moves slowly but steadily from the site of the infective wound toward the organs of the central nervous system. The initial symptoms give little indication of the horror to come. Among the early signs of clinical rabies—irritability, fatigue, malaise, and other nonspecific forms of distress—perhaps the most common (though even they are by no means universal) are pain at the site of the infective wound and severe headache. Within a few days, more obvious indications of central nervous system

involvement begin to manifest themselves. Difficulty in breathing, severe pain in the stomach or chest, and extreme hypersensitivity to visual stimuli (especially bright or shimmering objects) often appear as the disease continues its relentless course. Perhaps the most distinctive feature of the disease, present in the majority of rabies patients, is a pronounced aversion to liquids, which the victim often pushes aside even when desperately thirsty. This symptom gives rabies its other familiar name, "hydrophobia" (or fear of water)—though the fear is not of water per se, but rather of the pain, choking, gagging, and convulsions induced by trying to swallow the shimmering liquid.

By the time the virus reaches the brain, the effects are often such as to make its victims behave like "mad" animals themselves. An appreciable minority (perhaps 20 percent) of rabies patients exhibit a predominantly "dumb" or quiet and paralytic form of the disease. But most suffer from the "furious" form marked by episodes of extreme hyperactivity, convulsions, thrashing, hallucinations, excessive salivation, and spitting. A few even howl like forlorn dogs and try to bite anyone within reach. The quiescent periods that separate these episodes of bizarre behavior are in some ways worse yet. For the pitiful victims then often display an almost eerie lucidity, a heightened sense of affection toward relatives and others, and an exquisitely human awareness of their impending death.

Of the many horrifying features of rabies, surely the most dreaded and dreadful is its uniformly fatal outcome. Once the symptoms become manifest, once the disease has "declared" itself, the mortality rate is effectively 100 percent.[10] The only merciful feature of rabies is that its clinical course is fairly brief—the final stupor and coma ordinarily come within a few days of the outbreak of symptoms. The immediate cause of death is usually cardiac arrest or respiratory collapse. At least until the advent of mechanical respirators, which in effect only prolong the agony, all that could be done for rabies patients was to make them as comfortable as possible, usually by placing them in a darkened room and otherwise reducing external stimuli. No one who has observed a rabies patient—certainly, no physician who has stood by helplessly as the disease took its toll—is likely to forget the experience, and there can be few more poignant stories in the annals of medicine than case histories of rabies. Some sense of the full horror of the disease is captured in the remarkable and pitiful case history of John Lindsay, weaver at Fearn Gore near Bury, England, first published in 1807 and reprinted in Appendix K. Listen, finally, to the testimony of the distinguished physician and belletrist Lewis Thomas. In late 1993, as he lay on his own deathbed, Thomas spoke of his belief that, in the final moments, death comes without agony, perhaps because the brain's last act is to release pain-killing opiates. He could think of only one exception from his clinical experience: death from rabies, where the agony never seemed to end.[11]

By now it should be clear that rabies, however rare, was an especially dramatic disease with which to begin the effort to extend laboratory-produced vaccines to human diseases. From the outset, Pasteur knew that he would be hailed as a savior if he succeeded in this quest.[12] Here above all he displayed the theatrical flair that marked his choice of subjects to pursue and his manner of presenting the results to an audience gripped with suspense and eager to hear a happy ending. As everyone knows, Pasteur did not disappoint them. The closing act of his work on rabies was an appropriately spectacular conclusion to an already remarkable career.

PASTEUR'S WORK ON RABIES FROM 1881 THROUGH 1884: THE LABORATORY NOTEBOOKS

But behind this last great public performance lay a long and often disappointing series of rehearsals. Here again Pasteur's private laboratory notebooks will serve as a central source. In this chapter, they will be used mainly to enrich, rather than replace, the story that emerges from Pasteur's published papers on rabies between 1881 and 1884. But the notebooks from this period also reveal a dramatic and important story that left no trace whatever in Pasteur's published work. That story, told here for the first time, concerns two hitherto unknown attempts by Pasteur to cure symptomatic rabies in human cases. And it turns out that the story of these two "private patients" may be linked with the single most celebrated achievement in Pasteur's career—the application of his rabies vaccines to young Joseph Meister in July 1885, as we shall see in Chapter Nine.

Pasteur's laboratory notebooks contain at least one passing reference to rabies as early as 1876. In August of that year, on a list of "books to buy," he included Joseph Enaux and François Chaussier, *Méthode de traiter les morsures des animaux enragés* (*Method of Treating the Bites of Rabid Animals*), describing it as a "good treatise to consult."[13] In this book, published nearly a century before (in 1785), Enaux and Chaussier ascribed rabies to a poison (virus) and endorsed the classic treatment of cauterizing rabid animal bites as soon as possible. But the book also contained an extended discussion of "malignant pustule," the name by which anthrax was known when it occurred in humans.[14] At this point, in 1876, Pasteur was almost certainly more interested in this part of the book than in its main topic of rabies. Most of the other books on his list concerned anthrax, including "all the works of Davaine."[15] And, as we have seen in the preceding chapter, Pasteur was just

then redeeming his long-standing pledge to begin the study of infectious diseases by focusing on anthrax.

It was not until mid-December 1880 that Pasteur began to make regular and sustained references to rabies in his laboratory notebooks. That is not to say that rabies had now become the central focus of his research. Far from it. We need only recall from the preceding chapter that just five months had passed since Toussaint had announced his discovery of a vaccine against anthrax, leading Pasteur and his collaborators to accelerate their research on that disease and to redouble their efforts to find their own vaccine against it. At a point when the famous Pouilly-le-Fort trial was still six months away, it can hardly be said that rabies had become Pasteur's dominant preoccupation. Nor did it become so for roughly three more years. In the meantime, Pasteur and his collaborators pursued research on a variety of other diseases. Besides anthrax and chicken cholera, they included septicemia, swine fever, peripneumonia, yellow fever, and "horse typhoid." Because Pasteur generally arranged his notebooks chronologically rather than topically, and because he and his collaborators were pursuing these several lines of research simultaneously, the notebook pages devoted to rabies are repeatedly interrupted by reports of work on other diseases. It is therefore often difficult to follow every twist and turn in the path of Pasteur's early research on rabies, and no systematic attempt to do so will be made here.

One thing, however, is perfectly clear. As Pasteur reported in January 1881, and as his laboratory notes confirm, his research on rabies began on 10 December 1880. On that day Dr. Lannelongue, a surgeon at the hospital of Sainte-Eugénie, informed him of the admission there of a five-year-old boy suffering from rabies. Pasteur went to see the boy at 5 o'clock that afternoon with his collaborators, Charles Chamberland and Emile Roux. They observed all the classic symptoms of declared rabies in this doomed little boy, who had been bitten on the face by a rabid dog a month before. The boy died at 10:30 the next morning, December 11. At 3 o'clock that afternoon, four hours or so after the boy's death, Pasteur used a painter's pencil to collect some mucus from his mouth. After being mixed with a small amount of ordinary water, the mucus was injected into two rabbits that were then transported to Pasteur's laboratory on the rue d'Ulm. Both rabbits succumbed to these injections within thirty-six hours.[16]

Over the next few weeks, Pasteur established that blood taken from the two rabbits could, in its turn, produce similarly rapid deaths with similar symptoms in other rabbits or dogs. He associated these deaths with a new microbe similar in form (a figure 8) to the chicken cholera microbe, but different in its physiological properties and pathological effects. He also managed to cultivate this new microbe in artificial cultural media.[17] In his laboratory notebook from this period, he sometimes referred to it as "the microbe of rabies,"[18] but that was almost surely out of convenience rather than conviction. Even in private, Pasteur never insisted upon any direct connection between this new microbe and rabies. His published accounts were even more circumspect. From the outset, in January 1881, he spoke only of "a new disease produced by the saliva of a child dead of rabies." Given the source of the saliva, he did not immediately dismiss the possibility that there might be some "hidden relation" between rabies and this new microbe, but he also stressed that the disease it produced—both in its symptoms and in the rapidity with which it killed rabbits and dogs—differed strikingly from ordinary rabies.[19] By March, Pasteur had found the new microbe in the saliva of healthy adults as well as in that taken from victims of diseases other than rabies.[20] He then firmly rejected any connection whatever between rabies and the new microbe—which he had now come to call the *organisme auréole* (the "organism with a halo") or simply the *microbe de salive*, the "saliva microbe."[21]

With this point established, Pasteur's interest in the new microbe declined sharply. He did later claim that the saliva microbe—like the chicken cholera and anthrax microbes—could be attenuated and a vaccine therefore produced by exposure to atmospheric air. But this alleged new vaccine had nothing to do with rabies and had little practical import of any sort. For by June 1881, when he announced the discovery of this vaccine, Pasteur had decided that the saliva microbe might well be entirely harmless to man, however lethal its effects when injected into rabbits or dogs.[22] Some latter-day students of Pasteur's work have identified his "saliva microbe" as a pneumococcus.[23] If so, he never recognized it as such himself.

As early as 26 January 1881 Pasteur referred in his laboratory notes to a search for "the organism of true rabies."[24] The locus of his search—in the brain tissue of rabies victims rather than in their saliva or blood, where the saliva microbe could be found—suggests that he even then very much doubted any direct link between rabies and the saliva microbe. But he did always suppose that a rabies microbe must exist and tried repeatedly to isolate it. His laboratory notes record moments of hope when he thought he had achieved that goal, but in the end he had to admit that the "true rabies microbe" continued to elude him.[25] In retrospect, we can say that Pasteur's search for this microbe was doomed to fail given the techniques at his disposal. For the rabies "microbe," like that of smallpox, is in fact a filterable virus, much too small to be detected by the microscopes then available and incapable of cultivation in any of the artificial cultural media known to Pasteur.

But Pasteur did not allow his failure on this front to block advance along other lines. With a flexibility born partly of necessity, he came increasingly to focus on a principle and technique that had played a decidedly secondary

role in his work on chicken cholera and anthrax. In that work, the main goal—and success—had been to cultivate and attenuate the implicated microbe in sterile artificial media, outside the animal economy. Yet Pasteur had also long conceived of living organisms as another sort of "cultural medium," and the ultimate success of his quest for a vaccine against rabies depended crucially on his skillful exploitation of this insight. Using by turns rabbits, guinea pigs, dogs, and monkeys, Pasteur made the nervous tissue, and especially the brain, of living organisms the medium in which to cultivate and hopefully attenuate the otherwise elusive "rabies microbe."[26]

Pasteur had at least one important predecessor in his work along these lines, the now forgotten veterinarian Pierre-Victor Galtier (1846–1908), who (like the ill-fated Toussaint of Chapter Six) had studied with Auguste Chauveau and ultimately became a professor at the Veterinary School of Lyon.[27] In 1879 Galtier reported that rabies could be transmitted experimentally from dogs to rabbits with a marked reduction in the incubation period of the disease—from perhaps a month on average in dogs to an average of eighteen days in his rabbits. This result almost literally doubled the number of experiments that could be performed within a given period of time. This advantage of rabbits—along with the fact that they were relatively cheap, safe to handle, and easy to keep—quickly made them the experimental animal of choice for students of rabies, including Pasteur. Galtier also suggested that the long incubation period of rabies raised the possibility that a preventive remedy might be applied after infection with the virus but before the symptoms broke out.[28] In 1881 Galtier reported that he had transmitted rabies experimentally to guinea pigs as well as rabbits and claimed that sheep could be rendered immune to rabies by the intravenous injection of saliva from rabid dogs.[29]

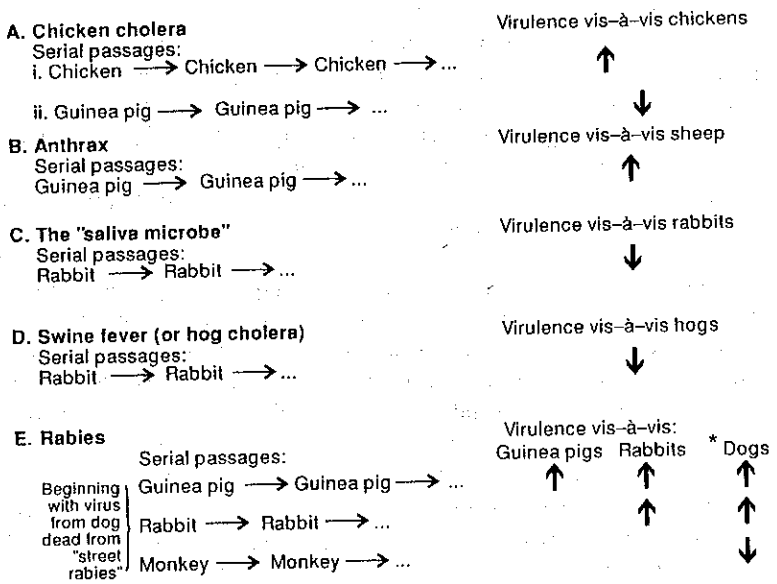
In his published work, Pasteur referred only once to this claim by Galtier—the first reported example of the experimental production of immunity against rabies—and even then only to cast doubt upon it.[30] Several years later, however, Pasteur's own leading collaborator on rabies, Emile Roux, publicly confirmed Galtier's claim that sheep could be rendered immune to rabies by the intravenous injection of saliva from rabid dogs.[31] By then, however, Pasteur had produced his own vaccines against rabies in dogs and man. Small wonder that Galtier's contributions have faded from view. Yet his work surely gave Pasteur reason to hope that his own efforts to produce immunity against rabies were not entirely baseless, and in any case Galtier had established the possibility and advantages of using rabbits and guinea pigs in rabies research.

Pasteur and Roux quickly seized the opportunities opened up by Galtier's work. And they soon went well beyond anything done by Galtier, who published nothing novel on rabies after 1881.[32] From the outset, Pasteur and Roux skillfully exploited an important finding that had emerged during their earlier work on chicken cholera and anthrax: namely, that the virulence of pathogenic microbes vis-à-vis a given organism could be altered by sequential (serial) passages through the same or other appropriate living organisms. The virulence of any microbe is relative to the organism to which it is applied and the organisms through which it is successively passed. Serial passages of a microbe through one species may increase its virulence vis-à-vis a given organism, while serial passages of the same microbe through a different species may decrease its virulence vis-à-vis that same organism. For example, as we shall see more fully below, the serial passage of the rabies virus through rabbits *increases* its virulence vis-à-vis both dogs and humans, while serial passage of the virus through monkeys *decreases* its virulence vis-à-vis both dogs and humans. In general, serial passage of a microbe within a given organism increases its virulence for that organism; for example, serial passage of the rabies virus through guinea pigs increases the virulence of the virus in successive guinea pigs.[33] (See fig. 7.1.)

Actually, this effect had been known before Pasteur focused his attention on animal diseases. His great German rival, Robert Koch, for one, had drawn attention to the increasing virulence produced by serial passages in his early work on anthrax and traumatic infectious diseases. But Koch supposed that serial passages increased the virulence of microbial cultures by enhancing their "purity"; in 1878, he described the technique of serial passages as "the best and surest method of pure cultivation,"[34] and did not imagine that the intrinsic properties of the microbe had thereby been changed. Pasteur, by contrast, had come to believe that the alterations in virulence produced by serial passages resulted from real changes in the properties of the microbe itself. Through exposure to different "cultures," Pasteur gradually realized, microbes could be quite fundamentally transformed in their physiological and pathological properties.[35]

In any case, by the time Pasteur took up the study of rabies, he knew that attenuated cultures of the chicken cholera microbe could regain their original virulence in chickens by repeated passages through young or small birds. Similarly, he knew that attenuated cultures of the anthrax bacillus could be made progressively more virulent in sheep by repeated passages through young guinea pigs. He and Roux doubtless expected a similar result in the case of rabies and therefore launched a systematic program of experiments in which the rabies virus was passed sequentially from rabbit to rabbit or guinea pig to guinea pig. In the process, the virulence of the rabies virus gradually increased vis-à-vis dogs as the incubation period of the disease gradually decreased. Ultimately, they found that the incubation period,

Ordinarily, the serial passage of a given micro-organism through another organism increases the virulence of the microbe vis-à-vis that organism. But this rule is by no means universal. In fact, the virulence of any given microbe vis-à-vis other organisms is relative. Hosts vary in their response to the invasion of microbes, and they sometimes decrease rather than increase the virulence of the invading microbes vis-à-vis themselves or other organisms. The following chart provides examples of both outcomes from Pasteur's own research.



* Although Pasteur never quite said so explicitly, he assumed that the immune response in dogs would be in the same direction for humans.

↑ Indicates increase in virulence (correlated with decrease in incubation period)

↓ Indicates decrease in virulence (correlated with increase in incubation period)

Figure 7.1. On the relativity of immune responses.

perhaps a month or more in "street rabies"—as Pasteur called the rabies in dogs that acquired the disease in the ordinary way (i.e., through the bites of rabid dogs)—could be reduced to about a week in rabbits by prolonged serial passages through rabbits.[36] Pasteur and Roux thus reduced by at least half again the already abbreviated incubation period that Galtier had

achieved in his earlier work on experimental rabies in rabbits and guinea pigs. In doing so, Pasteur and Roux further demonstrated the advantages of these animals in rabies research. More than that, as we shall see, the highly virulent and stable or "fixed" rabies virus that resulted from these serial passages through rabbits was eventually to become the starting point in the production of Pasteur's rabies vaccine.

But if the method of serial passages was the centerpiece of Pasteur's early work on rabies, he long kept it private. Three years passed before he disclosed any details of the technique in print. In fact, Pasteur was generally reticent about his work on rabies until mid-1884. Here again, as in his search for vaccines against chicken cholera and anthrax, Pasteur pressed onward with only occasional hints in public as to the nature and progress of his ongoing research. As late as February 1884, Pasteur had published only two brief papers on rabies. For the most part, however, the thin public record was this time in keeping with the actual state of affairs in Pasteur's laboratory. We must not forget that he and his collaborators were simultaneously at work on several other diseases, including notably anthrax. More important, their research on rabies had not yet brought much in the way of secure results. Partly because the presumed rabies microbe persistently eluded them, the Pastorians found rabies a difficult challenge.

Pasteur's notebooks throughout the first four years or more of his work on rabies provide a full and rich record of the often confusing, inconclusive, and frustrating results of this research. The notebooks also suggest that Pasteur's passion for order—in nature as in daily life—did not always serve him well in his work on rabies, where individual responses to pathogenic microbes tended to disrupt any neat pattern. Barely concealed beneath the laconic and meticulous records of his experiments is Pasteur's increasing impatience at the vagaries of disease as it manifested itself in real individual living organisms. This would have come as no surprise to a clinician—as it did not to Pasteur's medically trained collaborator, Emile Roux—but Pasteur found it frustrating. Living animals, it turned out, were rather crude and demanding "cultural media."

Pasteur's frustration becomes most evident in the notebook pages devoted specifically to efforts to find a vaccine against rabies. No attempt will be made here to give a systematic account of the early phases of this quest. But it does deserve saying even now that Pasteur's search for a rabies vaccine, like his earlier work on methods of brewing beer, was characterized by a remarkably empirical, hit-or-miss approach to the problem. Charting through the Byzantine maze of Pasteur's early laboratory notes on rabies, one eventually realizes that his basic procedure was simply to inject a variety of experimental animals—though mainly rabbits—with a wide range of

cultures or substances and then watch what happened. Through late 1883, Pasteur had tried the following techniques among others in his search for a rabies vaccine: injections of saliva or blood from rabid animals, sometimes in large quantities, sometimes in small; inoculations with filtered emulsions of rabid brain tissue; and injections of emulsified rabid tissue from the medulla oblongata that had previously been treated with hydrogen peroxide (*l'eau oxygène*), perhaps a reflection of the oxygen theory of attenuation he had conceived during his work on the chicken cholera vaccine. He even tried to protect animals against rabies by infecting them with anthrax.[37] In the end, none of these approaches fulfilled Pasteur's occasional expressions of confidence in one or another of them.

But if these and other failures ever tempted Pasteur to abandon his search for a vaccine, there was always the awful specter of rabies victims to revivify his efforts. Not even the usually aloof and outwardly gruff Pasteur could ignore or forget the horror of rabies, especially in children. His otherwise impassive laboratory notebooks sometimes take on a very different tone in the face of clinical rabies in children. A notebook entry in early November of 1883, for example, records the poignant story of a seven-year-old boy who was seized with a severe headache upon leaving school and fell into convulsions upon reaching home. The night before entering the hospital where he was very soon to die of rabies, this pitiful boy had a premonition of the disaster that awaited him and beseeched his mother not to leave him alone, embracing her in "very enthusiastic and prolonged caresses." Pasteur's notebook then reverted to its usual dispassionate tone as he recorded the effects of rabies in rabbits inoculated with brain tissue taken from this boy after his death.[38]

This and other recorded encounters with doomed rabies patients repeatedly stoked Pasteur's ambition to find a way to prevent all such scenes in the future. As he and his collaborators struggled fitfully toward that goal, Pasteur occasionally disclosed their most secure results, albeit sometimes after a substantial delay and almost always briefly and vaguely. It comes as something of a surprise to discover that the entire body of Pasteur's published work on rabies barely fills one hundred pages in print.

PASTEUR'S PUBLISHED PAPERS ON RABIES FROM MAY 1881 THROUGH AUGUST 1884

In May 1881, in his first published paper on rabies per se (as distinct from the "saliva microbe"), Pasteur reported that he and his collaborators had developed a new technique for transmitting the disease with certainty. Hitherto, research on rabies had been impeded by the fact that the disease was

not consistently transmitted either by the injection of rabid saliva or the bite of a rabid animal. More surprisingly, since it seemed clear that the nervous system and especially the brain was the ultimate seat of the disease, even subcutaneous injections of rabid nervous tissue did not always transmit the disease from one animal to another. Galtier himself had reported that such injections did not uniformly produce rabies in the recipient animal. Pasteur seized on Galtier's admission to emphasize that some doubt remained as to the anatomical locus of rabies and, ipso facto, the most reliable way of transmitting the disease experimentally. But, said Pasteur, he and his collaborators—actually, it was Emile Roux[39]—had at last developed a uniformly successful method of transmitting the disease from animal to animal. In this new method, cerebral matter was extracted from a rabid dog under sterile conditions and then inoculated directly onto the surface of the brain of a healthy dog through a hole drilled into its skull. Under these circumstances, Pasteur reported, the dog thus inoculated through its trephined skull invariably contracted rabies in less than three weeks, as compared to the average incubation period of a month in dogs that contracted rabies in the ordinary way through the bites of another rabid dog.[40]

More than eighteen months passed before Pasteur published a second paper on rabies. In this brief and often vague paper of December 1882, with "all details left aside for the present," Pasteur announced that rabies could also be reliably transmitted to previously healthy animals by intravenous injection. When transmitted this way, as distinguished from the previously announced method of intracranial inoculation, the virus usually produced rabies in its "paralytic" rather than "furious" form. Pasteur further claimed that the incubation period of the disease had now been reduced to somewhere between six and ten days, though he said nothing to indicate precisely how this result had been achieved. He reported that nothing had yet come of attempts to produce immunity against rabies by injecting saliva or blood from rabid animals into healthy ones. But he and his collaborators had happened upon a few dogs that were "spontaneously" or "accidentally" immune to rabies. When injected with a rabies virus that was virulent enough to kill other dogs, these innately "refractory" dogs also displayed symptoms of rabies, but then recovered from the disease and resisted subsequent injections of highly virulent rabies virus. This result established that rabies shared the distinguishing feature of the other "virus" diseases exemplified by smallpox: it did not recur in a host that had survived an initial attack of the disease. That rabies shared this feature of viral diseases had been far from certain since its victims almost always died. But Pasteur now insisted that a few "naturally" resistant dogs could indeed recover from relatively mild forms of symptomatic rabies, after which they remained forever immune to the disease. And this result encouraged hope that the search

for a vaccine against rabies might eventually succeed. Pasteur concluded his paper by reporting that he and his collaborators had now carried out more than two hundred experiments on rabies in pursuit of this goal.[41]

Several hundred more experiments had been completed, with the sacrifice of several hundred more animals, by the time Pasteur published his third paper on rabies after another interval of more than a year. By this point, in February 1884, Pasteur and his collaborators had been at work on the disease for more than three years. The two papers published thus far had been brief and tantalizingly vague. Only Roux's technique of transmitting rabies by intracranial inoculation through a trephined skull had been described in any detail—though Pasteur's laboratory notebooks make it clear that even this technique did not invariably succeed.[42] But now, quite suddenly, in his third published paper on rabies, Pasteur claimed that he and his collaborators were well on their way to a solution to the problem of rabies.

In this third paper, delivered to the Académie des sciences on 25 February 1884, Pasteur did concede that he and his collaborators had still not managed to isolate and cultivate a rabies microbe in artificial media, though he continued to presume that one must exist. Insisting that a rabid brain could easily be distinguished from a normal one by the presence of numerous fine granules in the rabid medulla, he hoped that he would eventually be able to prove that these granulations were "actually the germs of rabies." But whatever the outcome of further attempts to isolate the rabies microbe, there was already much more exciting news to report. For Pasteur claimed that he and his team had now found a "method of rendering dogs resistant to rabies in numbers as large as desired." The point of departure for the new method, he reported without elaboration, was the production of rabies viruses of varying degrees of virulence. He further disclosed that he now had on hand twenty-three dogs capable of withstanding injections of the most virulent rabies virus. In principle, the problem of preventing rabies in man had also now been solved, since the dog was the ultimate source of the disease. Moreover, the lengthy incubation period of rabies gave reason to hope that a bite victim could be rendered immune before the symptoms became manifest.[43]

Three months later, on 19 May 1884, Pasteur gave a somewhat fuller account of the methods by which he and his collaborators had prepared the rabies virus in varying degrees of virulence. Pasteur now publicly disclosed, for the first time, their technique of increasing the virulence of ordinary canine rabies by serial passages through guinea pigs or rabbits. In both species, serial passages led to a gradual increase in virulence and an associated decrease in the incubation period of the disease. The shorter the incubation

period, the more virulent the virus that produced it. As the virus was passed sequentially from guinea pig to guinea pig or rabbit to rabbit, the incubation period steadily declined toward a stable minimum—roughly a week in the rabbit—that corresponded with a stable or "fixed" maximum in virulence. Pasteur had reported as early as December 1882 that the incubation period in his experiments had already reached six to ten days instead of the month typical of ordinary "street rabies" in dogs. But only now, seventeen months later, did he disclose the method by which this result had been achieved.[44]

In this same paper of May 1884, Pasteur also revealed that he and his collaborators had found an organism in which serial passages produced the opposite effect on the rabies virus—decreasing rather than increasing its virulence. Actually, this attenuating effect of serial passages, like its inverse, had already been noticed and exploited during Pasteur's earlier work on other diseases. Specifically, Pasteur had found that the virulence of the saliva and swine fever microbes could be decreased as well as increased by serial passage through appropriate living organisms. Successive passages of the saliva microbe through the guinea pig, for example, made the microbe less virulent for rabbits. This result, published in September 1882, suggested the possibility that an attenuated culture—in a word, a vaccine—might be produced against any given microbial disease by successive passages of the implicated microbe through appropriate animals.[45] In November 1883, Pasteur reported that precisely this method had been used to produce a new vaccine against swine fever. The crucial step in the production of this vaccine had been the discovery that the swine fever microbe could be attenuated to the point of harmlessness for hogs by several passages through rabbits.[46]

In the case of rabies, Pasteur now reported in his paper of May 1884, the virus could be attenuated for dogs by passing it from dog to monkey and then successively from monkey to monkey. After just a few such passages through monkeys, he claimed, the rabies virus became so attenuated that its hypodermic injection into dogs never resulted in rabies. Indeed, it sometimes produced no effect even when transmitted to dogs by Roux's supposedly infallible method of intracranial inoculation. At some point in its serial passage through monkeys, the rabies virus lost its virulence for dogs and began instead to protect them from the effects of somewhat more virulent strains of the virus, which in their turn acted as vaccines against still more virulent strains until eventually dogs could be rendered immune to even the most lethal virus. If all dogs were vaccinated in this way, rabies could eventually be eliminated. But until that "distant period," wrote Pasteur, there was an obvious need for a means of preventing rabies in humans after the bite of a rabid animal. He then created great excitement by reporting that his

first attempts along this line in monkeys seemed highly promising. He went so far as to say that "owing to the long incubation, I believe that we will be able to render [human] patients resistant with certainty before the disease becomes manifest." But he also emphasized that "proofs must be collected from different animal species, and almost ad infinitum, before human therapeutics can be so bold as to try this mode of prophylaxis on man himself."[47]

Pasteur closed his paper of May 1884 with a characteristic request that an official commission be appointed—in this case by the minister of public instruction—to validate the results of his research on rabies. He proposed to have this rabies commission begin its work by observing two sets of experiments that bore a striking structural resemblance to the famous Pouilly-le-Fort trial of his anthrax vaccine. First, he suggested, twenty of his vaccinated dogs should be placed with twenty unvaccinated dogs and all forty should then be subjected to the bites of rabid dogs. Second, the same experiment should be performed, except that the forty dogs should be infected with rabies through the almost infallible method of intracranial inoculation instead of through the bites of rabid dogs. Echoing almost perfectly the bold prophecy he had issued before the Pouilly-le-Fort trial, Pasteur predicted that "not one of my twenty [vaccinated] dogs will contract rabies, while the twenty control animals will."[48]

The proposed commission was duly appointed within a month. Among its members were several of Pasteur's leading colleagues and supporters from the Académie des sciences. Its chairman was his now long-standing convert, the veterinarian Henri Bouley, who had also played an important role in the Pouilly-le-Fort trial three years earlier. This French rabies commission published its initial report on 4 August 1884.[49] After two months of experiments whose results were reported to it by Pasteur, the commission found that none of his twenty-three vaccinated dogs had contracted rabies—whether from the bites of rabid dogs or from Roux's method of intracranial inoculation of the rabies virus. By contrast, two-thirds of the unvaccinated control dogs had already become rabid.[50] What the commission did not report in any detail—nor could it, since Pasteur had not supplied the pertinent information—was the method or methods by which his "refractory" dogs had been made immune. Like other readers of Pasteur's published papers, the commission members presumably supposed that his "refractory" (i.e., immune) dogs had been injected first with a rabies virus attenuated by serial passages through monkeys and then with progressively more virulent strains of the virus.

A week later, in a major address of 10 August 1884 to the International Congress of Medical Sciences at Copenhagen, Pasteur proudly cited this report of the French rabies commission in support of his claim that "rabies

is no longer an insoluble riddle." Situating his work on rabies in the context of a wide-ranging and triumphant discussion of the growing evidence for his germ theory of disease, Pasteur admitted that his audience "must be feeling a great blank in my communication; I do speak of the micro-organism of rabies." The reason for the omission, he continued, is that "we have not got it. . . . long still will the art of preventing disease have to grapple with virulent maladies whose micro-organic germs escape our investigation." Nonetheless, Pasteur reported, he and his collaborators had made major strides toward solving the rabies problem. Now, at last, he described in some detail the method of intracranial inoculation and his method of preparing the rabies virus in varying degrees of virulence. He stressed that the search for an attenuating medium for the virus had been long and frustrating. Through hundreds of experiments, the animals selected as potential attenuating organisms proved instead to increase rather than attenuate the virulence of the rabies virus. Not until December 1883 had he and his team turned to the monkey and uncovered its capacity to attenuate the rabies virus. As in his paper of May 1884, Pasteur asserted that the inoculation of a rabies virus attenuated by serial passage through monkeys, followed by increasingly virulent strains of the virus, could produce a "completely refractory state" in dogs. The only obstacle to the application of this method in human cases, wrote Pasteur, was that experimentation, "if allowable on animals, is criminal in man."[51]

Once again more than a year passed before Pasteur gave another public account of his work on rabies. The next paper, delivered to the Académie des sciences on 26 October 1885, created an immediate sensation and has lived in legend ever since. It described the application of a remedy for rabies to two boys—Joseph Meister and Jean-Baptiste Jupille—who had been badly bitten by rabid dogs. This paper was filled with human drama, but even it failed to convey the full range of hope, doubt, and anxiety that Pasteur had experienced since his last public communication on rabies. Among other things, as we shall see in Chapter Nine, this famous paper gave a very misleading impression of the animal experiments that preceded the application of Pasteur's remedy to young Meister and Jupille. In this and several other respects, there are some remarkable discrepancies between the public and private versions of this celebrated story.

One such discrepancy is astonishing. It has to do not with animal experiments, but rather with two hitherto unknown cases of human experimentation that preceded Pasteur's application of his rabies vaccine to human subjects. Unlike the stories of Meister and Jupille, these two cases have left no traces in the public record. They are recorded only in Pasteur's laboratory

The charts below indicate, in chronological order, the date of publication of each of Pasteur's papers on the "saliva microbe" and on rabies per se, and a brief statement of the basic results presented in each paper.

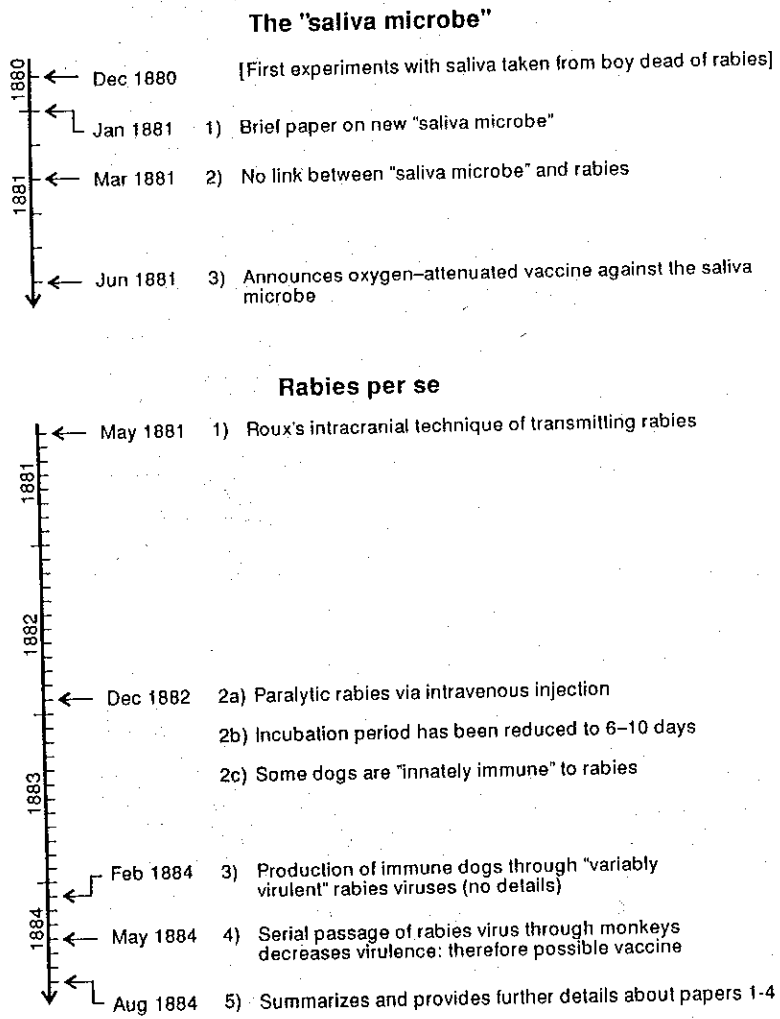


Figure 7.2. Pasteur's path to his rabies vaccine: the published papers.

notes. In these two cases, it can hardly be said that Pasteur's public statements were misleading, for in fact he wrote nothing about them at all. What follows is the first published account of two attempts by Pasteur to cure rabies in patients already displaying symptoms of the disease.

PASTEUR'S "PRIVATE PATIENTS"

On the first day of May in 1885, an otherwise ordinary sixty-one-year-old Parisian named Girard presented himself at the gate of the Necker Hospital in a highly agitated state.[52] He feared he had rabies and was admitted to the service of one Dr. Rigal. Within hours, in his laboratory on the rue d'Ulm, Pasteur received a telegram informing him of Girard's admission to the hospital. The telegram came to him from Dr. Georges Dujardin-Beaumetz (1833–1896), a member of the Académie de médecine and of the Council on Hygiene and Public Health of the department of the Seine. Since 1881 Dujardin-Beaumetz had been charged with investigating and confirming all cases of rabies in the department. By order of the prefect of police, the director of each hospital in Paris was required to notify Dujardin-Beaumetz of every admission for rabies. He then conducted an inquiry into each case of suspected rabies, reporting his results to the Council on Hygiene and Public Health.[53] When he informed Pasteur of Girard's admission to the Necker Hospital, Dujardin-Beaumetz knew that the celebrated scientist from the Ecole Normale was in eager pursuit of a rabies vaccine. He presumably sent the telegram in hopes of somehow advancing that cause.

At 10 o'clock on the morning of 2 May 1885, Pasteur went to see Girard with the attending physician, Dr. Rigal. Girard told them that he had been bitten on the knee by a wandering dog sometime in March. His wound had been thoroughly cauterized and had healed without difficulty. He had been well until now. He spoke very lucidly but complained of a severe headache and stomach pain. He drank a large cup of milk but could not bear the sight of water or wine. His legs shook and he could not eat. That same afternoon, having secured authorization to do so from Dr. Rigal, Pasteur returned to the hospital with two of his associates, Adrien Loir and Dr. Emile Roux. When they reached Girard, only an orderly (*interne de garde*) remained on duty with him. Pasteur and his assistants then exposed the right side of Girard's body and injected him with one full Pravaz syringe (one cubic centimeter) of a preparation they had brought with them from the laboratory on the rue d'Ulm. Since Pasteur was not medically qualified, the actual injection was presumably performed by Roux.

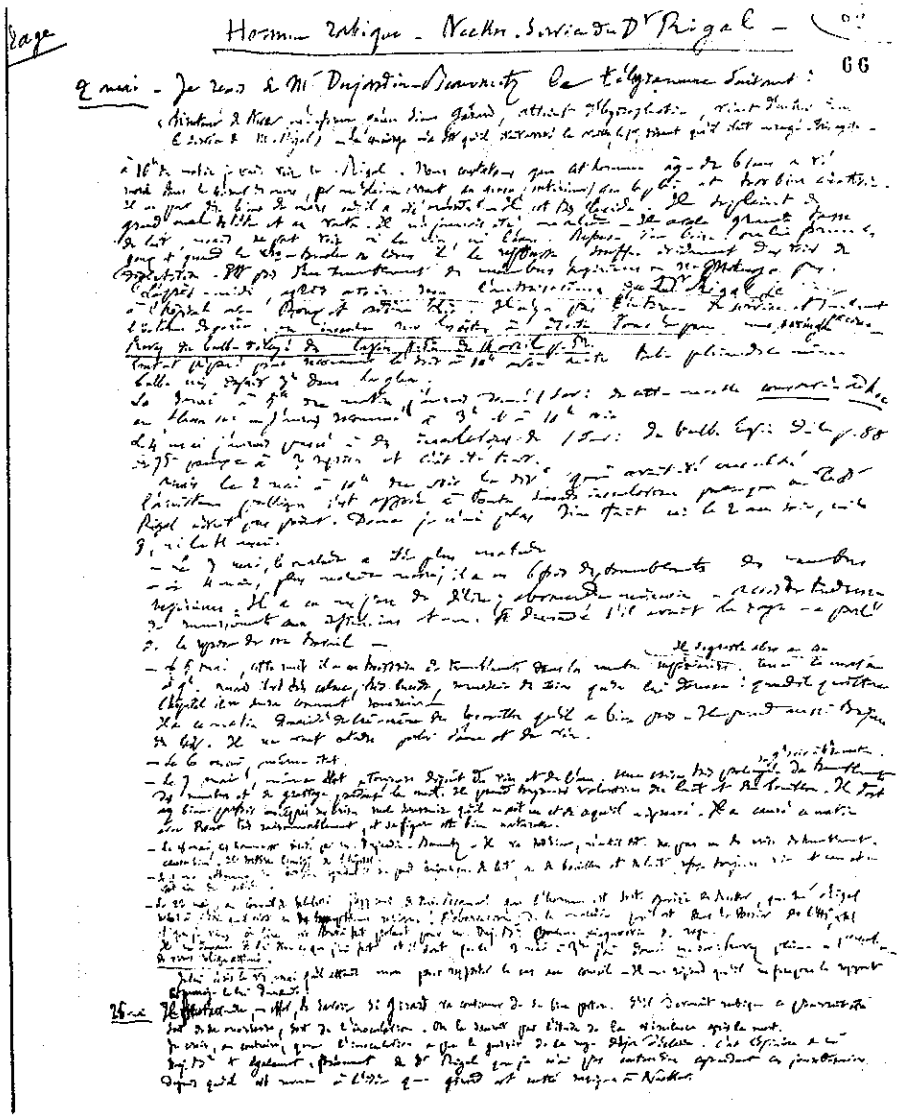


Figure 7.3. Pasteur's laboratory notes on the presumably rabid M. Girard, his first "private patient." The record begins on 2 May [1885]. Pasteur, *Cahier 94*, fols. 62–62v (using Pasteur's handwritten pagination). (Papiers Pasteur, Bibliothèque Nationale, Paris)

Pasteur and his collaborators then made the necessary preparations to repeat this injection into Girard at 10 o'clock that night. In fact, they planned to give him a series of six additional injections over the next two days, of which the first was to be identical with the one he had already received. The subsequent five injections were to be made with preparations that differed from the first in degree of virulence. In the event, however, these plans were thwarted by the public authorities. At 10 o'clock on the night of that same day, 2 May, Pasteur returned to the hospital to oversee Girard's second injection. But during the several hours he had been absent, the hospital authorities had evidently become concerned about the propriety of the afternoon's events. For some reason, at any rate, they had consulted with the Ministry of Public Assistance, and Pasteur was now told that Girard could undergo no further injections in the absence of his attending physician, Dr. Rigal. Girard was then abandoned to his fate without further treatment.

The outcome was remarkable. On 3 May, the day following his injection, Girard's condition deteriorated, and it was still worse the day after that. His arms trembled, he was in pain, and he asked if he had rabies. During the night of 4 May he was seized with fits of trembling in his upper limbs, at which time he also rubbed his neck. Yet another trembling fit struck him the next morning at 9 o'clock. When it ended, though, he was very calm and lucid, expressing appreciation for the care he had received. He asked for bouillon and consumed it without difficulty. He also drank some milk, but still wanted to hear nothing of wine or water.

Girard remained in the same general condition until 9 o'clock on the night of 6 May, when he suffered a prolonged attack of trembling in his limbs, during which time he also scratched at his body. This attack lasted until 4 o'clock the next morning, but he took milk and bouillon that day too. He also slept well enough at times, though he was disturbed by a nightmare about all that he had suffered. On the morning of 7 May he conversed rationally with Roux, and his countenance seemed normal. On 8 May Dujardin-Beaumetz visited Girard and found him doing well. He had experienced no further attacks of trembling and spoke lucidly. A week had passed since Girard's admission to the hospital, and his condition was now such as to give hope that he might soon be released. He seemed equally well on 9 May, though even then he continued to consume only milk and bouillon, rejecting wine and water as well as all solid food.

Two weeks later, on 22 May 1885, at a meeting of the Paris Council on Hygiene and Public Health, Pasteur learned from Dujardin-Beaumetz that Girard had been discharged from the Necker Hospital, presumably having

been cured. Dujardin-Beaumetz also reported that Dr. Rigal, who had become skeptical of the original diagnosis of rabies, was once again prepared to endorse it. In Dujardin-Beaumetz's own judgment, the diagnosis of rabies was fully justified by the hospital dossier and other evidence. Finally, Dujardin-Beaumetz asked Pasteur to specify the nature of the injection given Girard on 2 May. In his response, presumably solicited for inclusion in one of Dujardin-Beaumetz's reports to the Council on Hygiene and Public Health, Pasteur disclosed only that the injection had consisted of "one full Pravaz syringe [i.e., one cubic centimeter] of attenuated rabies virus." He did not specify the method by which this attenuation had been achieved.

The next day, 23 May 1885, Pasteur sent Dujardin-Beaumetz a letter asking him to postpone his report on Girard to the Council. Dujardin-Beaumetz immediately agreed to honor Pasteur's wishes. Before any such report was sent, Pasteur wanted enough time to have passed so that no doubt could remain that Girard might yet succumb to rabies. If Girard did eventually die of rabies, Pasteur continued, it would be important to determine whether his death had resulted from the dog bite or rather from the injection he had received at the Necker Hospital. That issue could be settled by transmitting tissue from Girard's brain to susceptible animals and then observing whether their clinical response was typical of ordinary rabies or rather of the altered virus that had been injected into him by Pasteur and his collaborators. But Pasteur did not think it would come to that. On 25 May 1885, in his laboratory notebook, he recorded his belief that the injection of 2 May had cured Girard of symptomatic rabies.[54]

Within a month, Pasteur was treating a second case of "declared" rabies, this time in an eleven-year-old girl named Julie-Antoinette Poughon. She had been bitten on the upper lip by her own puppy sometime in May and had been admitted to the Hospital of St. Denis on the morning of 22 June 1885 after suffering for two days from severe headache. Pasteur and the doctor in charge of her case agreed that she was clearly suffering from rabies. At Pasteur's suggestion, her doctor injected Julie-Antoinette with one full Pravaz syringe of a substance previously prepared in Pasteur's laboratory. At midnight she was given a second injection, which differed from the first in degree of attenuation. The next morning, 23 June, Pasteur returned to the Hospital of St. Denis at 10 o'clock with his nephew Adrien Loir. They barely reached Julie-Antoinette before she died at 10:30. The symptoms of rabies had quickly overtaken her despite the two injections of the previous day.[55]

The dramatic stories of Girard and Julie-Antoinette find no trace whatever in the published record. Except in his laboratory notebook and in his correspondence with Dujardin-Beaumetz, Pasteur never wrote about them

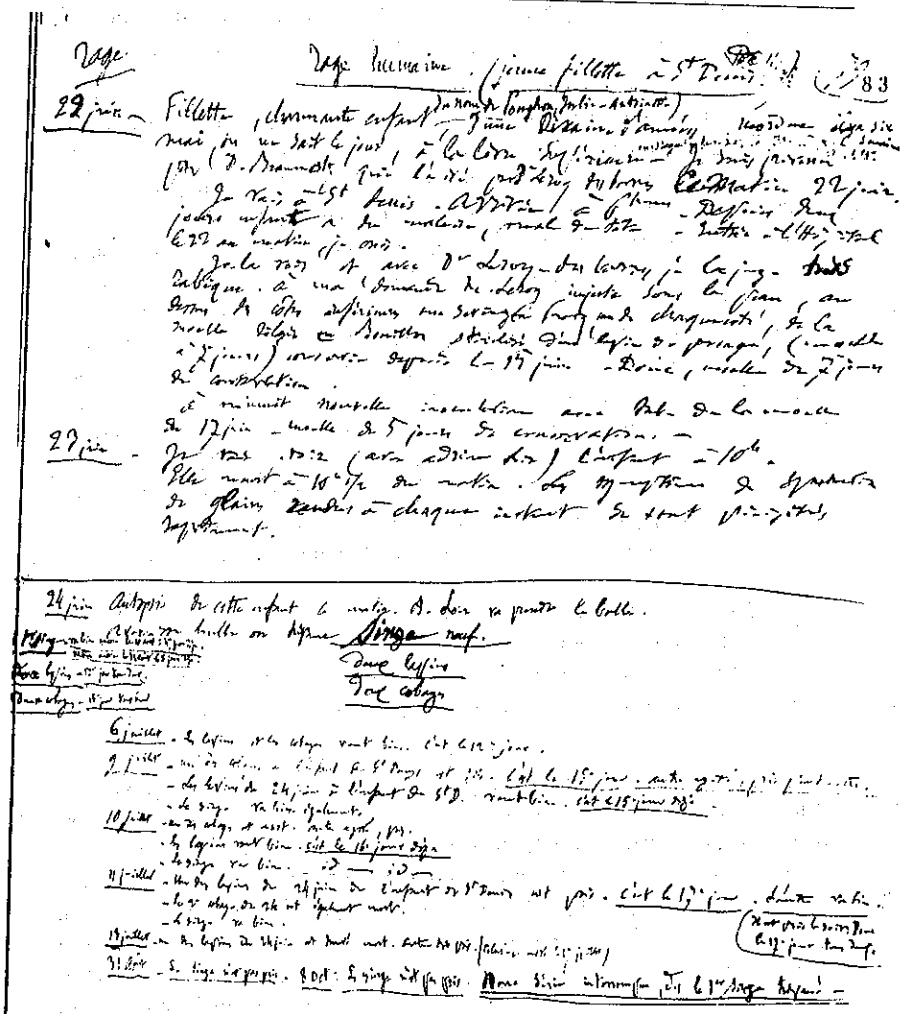


Figure 7.4. Pasteur's laboratory notes on Julie-Antoinette Poughon, his second "private patient." The record begins on 22 June [1885] and ends just a day later with an entry reporting the girl's death from rabies. Pasteur, *Cahier 94*, fol. 79 (using Pasteur's handwritten pagination). (Papiers Pasteur, Bibliothèque Nationale, Paris)

at all. Of Julie-Antoinette, there was perhaps little to be said. She had died of rabies despite Pasteur's desperate efforts to save her. But the public silence about Girard is impossible to understand unless Pasteur somehow came to doubt the reality of his alleged cure. Had he continued to believe that he had cured Girard, it is unthinkable that Pasteur would have kept such a monumental achievement out of the public eye.

Unfortunately, Pasteur's laboratory notebook tells us nothing about Girard's subsequent fate. The page devoted to the case ends abruptly on 25 May 1885 with the assertion that Drs. Rigal and Dujardin-Beaumetz now shared Pasteur's belief that his injection had cured Girard of symptomatic rabies. Something obviously happened later to destroy that belief, but Pasteur's notebook does not reveal what it was.[56] So a puzzle remains. It is unclear from the documents cited here whether or not the Girard treated by Pasteur died of rabies, and if so, exactly when. But that may not be an especially crucial point. For if this Girard did evéntually die of rabies, his death must have come at a point when Pasteur had already ceased to believe in his cure, thus helping to explain his apparent lack of interest in the news. And even if this Girard was still alive on 23 June 1885, Pasteur would have had another powerful reason for abandoning his belief in Girard's cure: the death of young Julie-Antoinette Poughon despite Pasteur's attempt to cure her by a method very similar to that used in the case of Girard.

Pasteur's real, if temporary, belief that he had cured Girard of symptomatic rabies is testimony to the power of wishful thinking in the face of dread disease. There was astonishingly little basis for that belief in any of Pasteur's animal experiments to that point, as we shall see. But quite apart from the results of his animal experiments, Pasteur's belief that he had cured Girard of clinical rabies would have been met with profound skepticism for another reason—namely, the uncertainty surrounding the diagnosis of rabies. Had Pasteur published an account of his alleged cure of Girard, the vast majority of physicians would have scoffed at the diagnosis. For death within days of the outbreak of symptoms had always been part and parcel of the very definition of rabies. In effect, "recovery" from clinical rabies was a contradiction in terms. Indeed, Girard's own attending physician, Dr. Rigal, at least briefly disavowed his initial diagnosis of rabies when Girard showed signs of recovering.[57] Other physicians would have been more insistent still that Girard must have suffered from another disease.

Pasteur himself later pointed out some of the uncertainties surrounding the diagnosis of rabies. Two years after *l'affair Girard*, for example, he spoke to the Académie des sciences about several cases of "false rabies." Relying on the authority of one Dr. Trousseau, Pasteur cited two cases in which symptoms of the disease had been induced solely by fear. In one case, a man suddenly displayed several of the classic features of rabies—including throat spasms, chest pain, extreme anxiety, and other nervous symptoms—merely because the disease had become the subject of a lunchtime conversation. And this man had never even confronted a rabid animal. Presumably more common was the second case, that of a magistrate whose hand had long before been licked by a dog later suspected of rabies. Upon learning that several animals bitten by this dog had died of rabies, the magistrate became extremely agitated, even delirious, and displayed a horror of water. His symptoms disappeared ten days later, when his physician persuaded him that he would already be dead had he been afflicted with true rabies.[58]

In this same address, Pasteur commented upon a recently published case history of "false rabies." Partly because it includes an arresting account of the classic symptoms of rabies, his commentary deserves quoting at length. As recorded in the *Comptes rendus* of the Académie des sciences for 17 October 1887, Pasteur spoke as follows:

> The patient to whom Mesnet refers in his brochure was an alcoholic who, having seen some sort of deposit in his glass during lunch, was seized by a feeling of horror toward the liquid and by a constriction of the throat, followed by headache and by lameness and fatigue in all his limbs. He spent Sunday in this state.
>
> During that night and during the day on Monday and Tuesday, no sleep, a fit of suffocation, throat spasms, and a horror of liquids, which he pushed aside in his glass. His countenance expressed disquiet. His eyes were fixed, glazed, the pupils greatly dilated. His speech was brief, jerky, rapid. He had difficulty breathing. When he was offered a glass of water, he pushed it aside with terror, and suffered fits of suffocation and of constriction of the throat. Bright objects and light were particularly disagreeable to him. He was painfully affected when the air was agitated in front of his face. He died Wednesday night after having suffered from a violent delirium, with extreme agitation, howls and cries, extremely abundant salivation, spitting, biting his bedsheets, and trying also to bite the person taking care of him. In short, this man displayed all the features of furious rabies [*l'hydrophobie furieuse*]. But he did not die of rabies. He had never been bitten and on several occasions, at long intervals, had already displayed symptoms analogous to false rabies. This man was an alcoholic and belonged, moreover, to a family in which one member had died of insanity [*aliénation mentale*].[59]

By October 1887, when he gave this address, Pasteur had a vested interest in emphasizing the difficulty of diagnosing rabies. For he was then defending himself against allegations that his rabies vaccine not only sometimes

failed to protect those who submitted to it, but in some cases was itself the cause of rabies and therefore death. A few hostile critics were insisting that some people died of rabies not only *despite* Pasteur's vaccine but *because* of it, and they tried to make Pasteur and his treatment responsible for the death of anyone who displayed any symptoms of nervous disease. In defense of his vaccine, Pasteur now emphasized the extent to which symptoms like those of rabies could appear in patients who did not have the disease. He therefore insisted that a diagnosis of rabies could only be established with confidence by experiments in which tissue from the victim's brain was transmitted to animals susceptible to the disease.[60]

But the uncertainty surrounding the diagnosis of rabies, which here served Pasteur's interests, could equally well have been turned against him had he publicized his alleged cure of Girard. In Girard's case, or in any other case of apparent recovery from rabies-like symptoms, no reliable diagnostic test existed. The animal experiments that Pasteur and others considered the most reliable diagnostic tool could be performed only after the death of a presumably rabid patient. Only then could nervous tissue be extracted from the patient's brain and injected into susceptible animals to see if they succumbed to rabies. Such postmortem tests obviously did nothing to reduce the uncertainty of diagnosing rabies in living patients.

Even today, rabies can be difficult to diagnose, as is made dramatically and tragically clear by four recent cases of human-to-human transmission of rabies through corneal transplants. In all four of these cases—two in Thailand, one in the United States, and one ironically in Pasteur's native region of France—the existence of rabies in the deceased corneal donors had gone unsuspected until the unfortunate recipients died of the disease. In two of the recipients, moreover, a firm diagnosis of rabies was not established until well after their deaths.[61] Rabies may seem to be a very distinctive clinical entity, but it can also be present in the absence of its usual dramatic symptoms, and at least some of those symptoms can appear in the absence of the disease. And if rabies can be missed even today despite the full panoply of current histiological and immunological diagnostic techniques, it was obviously much more difficult to diagnose in Pasteur's day.

All of this suggests that Pasteur would have faced a no-win situation had he tried to persuade others that he had cured Girard of rabies. Only if Girard died of rabies would most physicians have accepted the diagnosis in the first place. But in that case, of course, Pasteur's "cure" would have failed. Small wonder, perhaps, that he never publicly disclosed his belief that he had cured Girard. And when young Julie-Antoinette Poughon died of rabies after submitting to a remedy very similar to Girard's "cure," even Pasteur himself may have decided that his first "private patient," M. Girard, had been just another example of mistaken diagnosis—of "false rabies," in short.

CONCLUSION

Pasteur's belief that he had cured Girard had no detectable basis in prior animal experiments. If Drs. Rigal and Dujardin-Beaumetz briefly joined Pasteur in that belief, it was surely because of his general scientific eminence. They doubtless presumed that he had good grounds for his claim, but they would have felt otherwise if they had had access to Pasteur's laboratory notebooks. Without those notebooks and in the face of Pasteur's reticence, they had no way of knowing exactly what substance had been injected into Girard or to what extent, and with what success, it had been tested on animals. Pasteur's letter to Dujardin-Beaumetz concerning Girard disclosed only that he had been injected with one cubic centimeter of "an attenuated rabies virus."[62] Had Pasteur told Drs. Dujardin-Beaumetz and Rigal the full story of his animal experiments up to that point, they would have been surprised to learn of the precise preparation he had applied to Girard and curious to hear exactly how he proposed to justify his confidence in his alleged cure.

Unlike Drs. Dujardin-Beaumetz and Rigal, we now enjoy the privilege of direct access to Pasteur's once-private laboratory notes on rabies. They reveal, first of all, that Girard had been injected with a preparation that Pasteur had not yet described in print—namely, an emulsified spinal cord that had been extracted from a rabbit dead of experimental rabies and left to dry in a sealed flask for roughly two weeks.[63] This desiccated spinal cord was, then, the source of that "attenuated rabies virus" to which Pasteur referred in his correspondence with Dr. Dujardin-Beaumetz. The laboratory notes further reveal that six weeks later, on 22 June 1885, young Julie-Antoinette Poughon was treated by the same method, that is, with an injection prepared from a dried rabid cord—in her case, to no avail.[64] In his published papers up to this point, Pasteur nowhere mentioned experiments with dried spinal cords. He had written only of attenuated rabies viruses produced by serial passage through monkeys. The preparations actually used on Girard and Julie-Anoinette would thus have come as a surprise to Drs. Dujardin-Beaumetz and Rigal—or anyone outside Pasteur's tiny inner circle.

Outsiders would have been still more surprised to learn that Pasteur had never tried, not even once, to cure symptomatic rabies *in animals* by *any*

method before he decided to treat Girard—or so it seems to me from an analysis of his laboratory notebooks. A few days *after* Girard's treatment had begun, Pasteur did try to cure a rabbit of symptomatic rabies, but the animal died three days after the first series of its injections.[65] In the six weeks that passed between this unsuccessful animal experiment and Pasteur's equally unsuccessful attempt to cure Julie-Antoinette Poughon, his laboratory notes record no other attempts to treat animals suffering from symptomatic rabies. At the least, there is no evidence that Pasteur undertook any sustained program of experiments to treat "declared" rabies in animals before he undertook his treatment of Girard and Julie-Antoinette Poughon.

What, then, are we to make of Pasteur's attempts to cure rabies in these two "private patients"? To begin with the obvious, they represent examples of human experimentation. More than that, M. Girard and Julie-Antoinette Poughon were treated by a method that had apparently never been successfully tested on animals with symptomatic rabies. Even so, it should be emphasized, there was nothing unethical about Pasteur's interventions in the case of these two apparently doomed rabies patients. Even in his day, the distinction between therapeutic experiments and unethical human experimentation was perfectly clear. Everyone agreed that "therapeutic experiments"—those undertaken in the hope of benefiting the person submitting to them—were fully justified.[66] Pasteur's desperate attempts to save Girard and Julie-Antoinette Poughon from "declared" rabies did not violate any accepted ethical standards.

Nor did Pasteur violate any ethical precept by declining to publish accounts of these two "clinical trials." Indeed, in the case of Girard, it might even be said that Pasteur properly resisted the temptation to issue a "premature" announcement of his presumed cure. The subsequent death of Julie-Antoinette, despite Pasteur's attempt to cure her by a similar method, probably led him to believe that the diagnosis of rabies had been mistaken in the case of Girard. By his reticence in the meantime, he had prevented false hopes of cure in other victims of symptomatic rabies.

Yet it is hard to resist the judgment that Pasteur—whatever his formal ethical obligations—would have performed a valuable public service had he ultimately revealed the full stories of his two "private patients." Had he done so, clinicians would have become aware of another and especially arresting example of the uncertainty surrounding the diagnosis and clinical features of rabies. Such a public disclosure would also have served ever after as a striking illustration of the power of wishful thinking in the face of dread disease. Instead, these episodes shared the fate of most unsuccessful clinical trials: they were buried along with Julie-Antoinette Poughon.

In the end, the stories of Girard and Julie-Antoinette may have a much greater and distinctly ironic significance. For they were closely linked, both in time and technique, with a radical shift in the approach by which Pasteur sought to develop a vaccine against rabies, as we shall see more fully in Chapter Nine. For now, let us merely highlight the suggestive chronological sequence. Pasteur undertook his treatment of Girard on 1 May 1885. Up to that point, he had used several different methods in his attempts to produce a safe and effective rabies vaccine for animals, with variable and confusing results. By the time he undertook his treatment of Girard, Pasteur and his collaborator Emile Roux were already beginning to focus on the injection into dogs of emulsified rabid spinal cords. But until May 1885 Pasteur usually injected the rabid spinal cords in a very different—indeed precisely opposite—sequence from the one he would eventually use.

On 28 May 1885, just three days after recording his belief that he had cured Girard, Pasteur launched a systematic program of animal experiments to try to produce a vaccine by what he called in his laboratory notebook "the other method" in comparison to what had gone before—as we will see in Chapter Nine. By 23 June 1885, when Julie-Antoinette Poughon died of rabies despite Pasteur's effort to cure her, he was growing increasingly confident about the results of this "other method" in animal experiments. And just two weeks later, on 6 July 1885, it was precisely this "other method" that Pasteur used for the first time in a human case when he undertook the treatment of the badly bitten but thus far asymptomatic boy named Joseph Meister.

In other words, there is circumstantial evidence to suggest that Pasteur's radical shift in approach—his sudden turn to the eventually successful "other method"—in the search for a safe and effective vaccine was inspired by his presumed cure of Girard. If so, Joseph Meister became just the first of thousands to benefit from what was almost surely a case of mistaken diagnosis. Even here, in the case of Pasteur's greatest triumph, it might thus seem that a "lucky mistake" had once again put him on the path to success. We shall see, however, that the story is vastly more complicated than this sketch might suggest. And when that story is read out full and clear, we will have new grounds for appreciating the very real wisdom in Pasteur's own famous maxim that "chance favors only the prepared mind."

EIGHT

Public Triumphs and Forgotten Critics: The Debate over Pasteur's Early Use of Rabies Vaccines in Human Cases

ON MONDAY, 6 July 1885, three frightened and unexpected visitors made their way to Pasteur's laboratory at 45 rue d'Ulm in Paris. They had come to Paris by train from a village in Alsace, where two days before, on 4 July, two of them had been attacked by a dog displaying all the classic signs of rabies. One of the victims was the dog's owner, a grocer named Théodore Vone. His dog had bruised his arms, but without penetrating his shirt or skin. Pasteur sent him home with the assurance that he had nothing to fear. The other two visitors were a nine-year-old peasant boy named Joseph Meister and his fretful mother, who had not been attacked by the dog but was there to be with her badly bitten son. The boy had been bitten a dozen times or more, with severe wounds on the middle finger of his right hand and on his thighs and calves, some of them so deep that he could hardly walk. His trousers had been ripped to shreds. His condition might have been worse yet—indeed, the still rampaging dog might have killed him—had he not been rescued by two men who cornered and captured the dog, which was then destroyed by its master, M. Vone. An autopsy of the attacking dog revealed that its stomach contained hay, straw, and chips of wood, as was typical of rabid dogs. The worst of young Meister's bites had been cauterized with carbolic acid by a local doctor, but not until twelve hours after the attack.[1]

In the afternoon of that same day, 6 July 1885, Pasteur went as usual to the weekly meeting of the Académie des sciences. There he spoke of young Meister to his Académie colleague E.E.A. Vulpian, who had often lent support to Pasteur's causes and was now a member of the French rabies commission that had been appointed the year before at Pasteur's request. Pasteur asked Dr. Vulpian to examine Meister in consultation with Dr. Joseph

Grancher, clinical professor of children's diseases at the Paris Faculté de médecine and a recent recruit to the Pastorian team. Upon examining the boy's wounds, Drs. Vulpian and Grancher concluded that he almost surely faced death from rabies.[2] Pasteur then decided to treat young Meister by a method that he had thus far tried only on dogs. Since the boy was reluctant to go to a hospital, Pasteur arranged for him and his mother to be installed at an annex of the laboratory two blocks away, on the rue Vauquelin. At eight o'clock that same night, 6 July, young Meister submitted to the first of thirteen injections he would undergo over the next eleven days. He survived the injections and escaped the death from rabies to which he had once seemed doomed.[3]

Three months later, on 16 October 1885, the mayor of the village of Villers-Farlay near Pasteur's home town of Arbois sent him the letter referred to at the beginning of the previous chapter. Mayor Perrot's letter told Pasteur of the brave fifteen-year-old shepherd, Jean-Baptiste Jupille, who had been attacked and badly bitten two days earlier by a rabid dog while protecting several younger boys. The selfless courage of young Jupille gained in drama from the sorry circumstances of his family. The Jupille family, which included four or five other children, had fallen on hard times after the father lost his arm in a railway accident. Upon losing his arm, the father also lost his job with the railroad company for which he was then working. And since he was declared personally responsible for the accident, he had received no compensation for the injury. To enable the family to survive, Mayor Perrot had named the father village policeman for Villers-Farlay, but the salary barely sufficed to sustain the family. Jean-Baptiste, the eldest Jupille child, had therefore been sent to work as soon as possible as a shepherd for a local farmer. And now the poor family faced the prospect of losing him to rabies.[4]

Pasteur received Mayor Perrot's first letter about Jupille on 17 October 1885, just one day after it had been sent. He responded immediately, telling the mayor the happy story of Joseph Meister and offering to treat young Jupille by the same method. Pasteur's letter continued as follows:

> I should tell you, however, that the conditions are less favorable in this case. According to your letter, Jupille was bitten on the 14th of this month. This letter will reach you on the 18th. The boy will get here the morning of the 20th or the night of the 19th. The bites will already be six days old [by then]; those of little Meister had been only sixty hours old, and I do not yet know from my experiments at what point following the moment of [rabid] bites I can begin the treatment. Nonetheless I ought to tell you that I have succeeded in rendering some dogs immune to rabies six and eight days after their bites. . . .

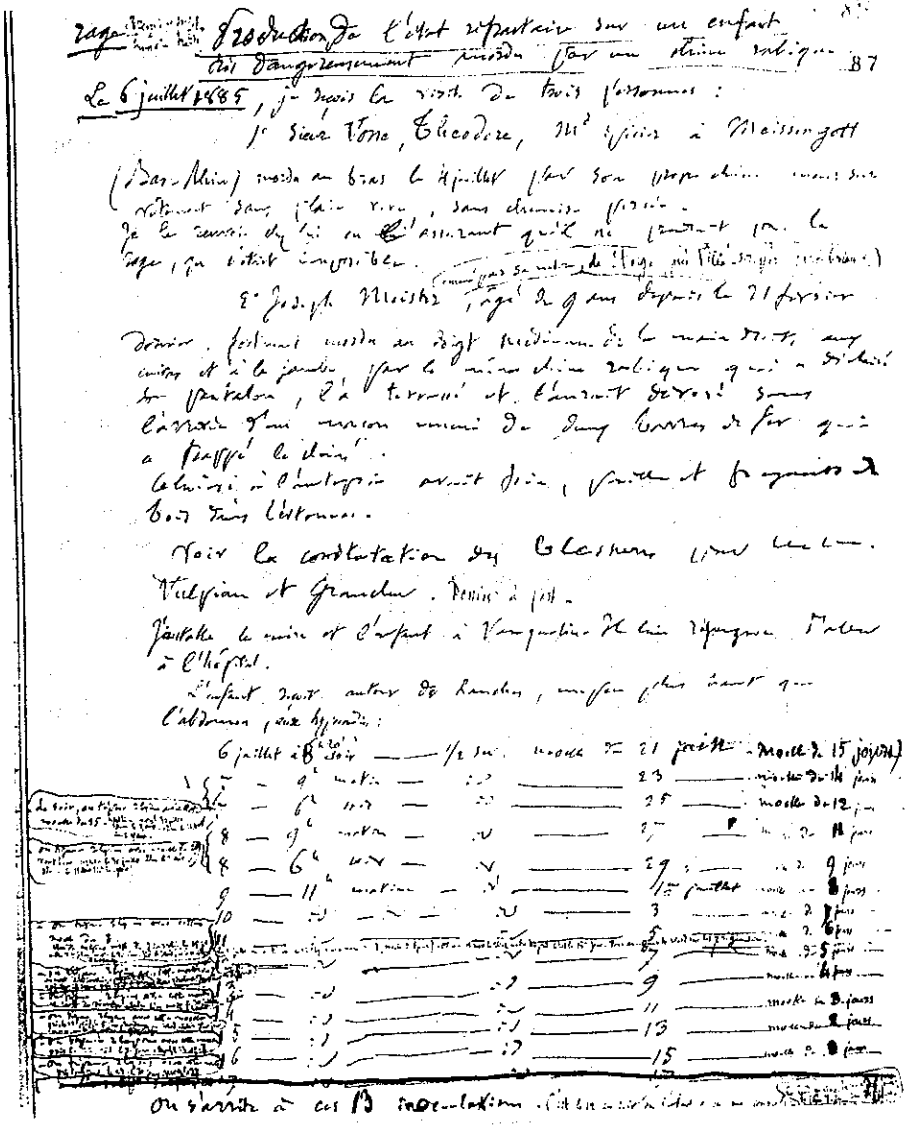


Figure 8.1a.

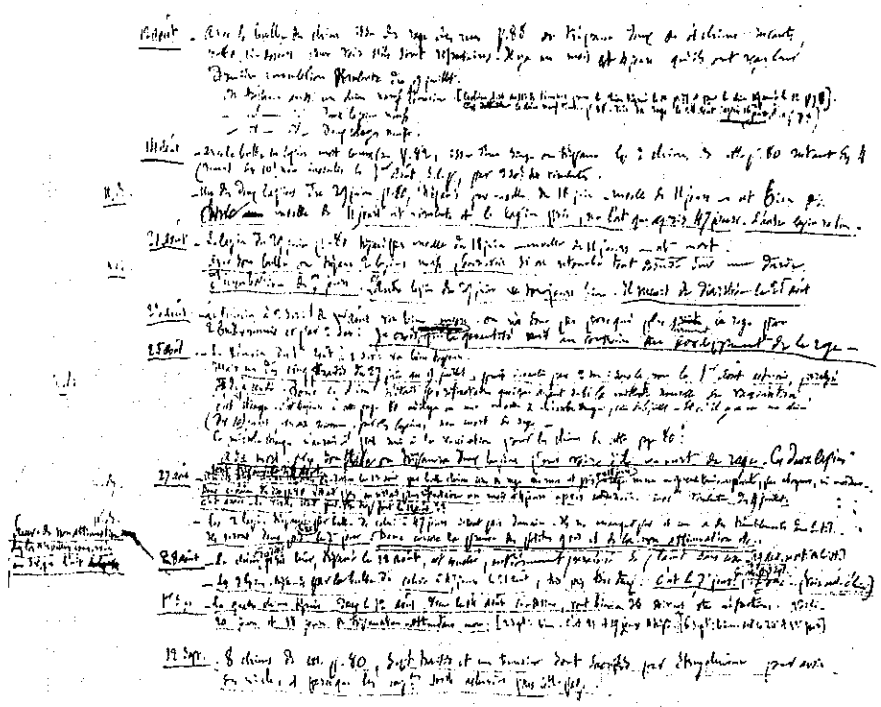


Figure 8.1 (a,b). Pasteur's laboratory notes on the treatment of Joseph Meister. The record begins on 6 July 1885. Not surprisingly, Pasteur gave special attention to these two pages in his notebook, beginning with the heading "Production of the refractory state in a child very dangerously bitten by a rabid dog." Pasteur, *Cahier 94*, fols. 83–83v (using Pasteur's handwritten pagination). (Papiers Pasteur, Bibliothèque Nationale, Paris)

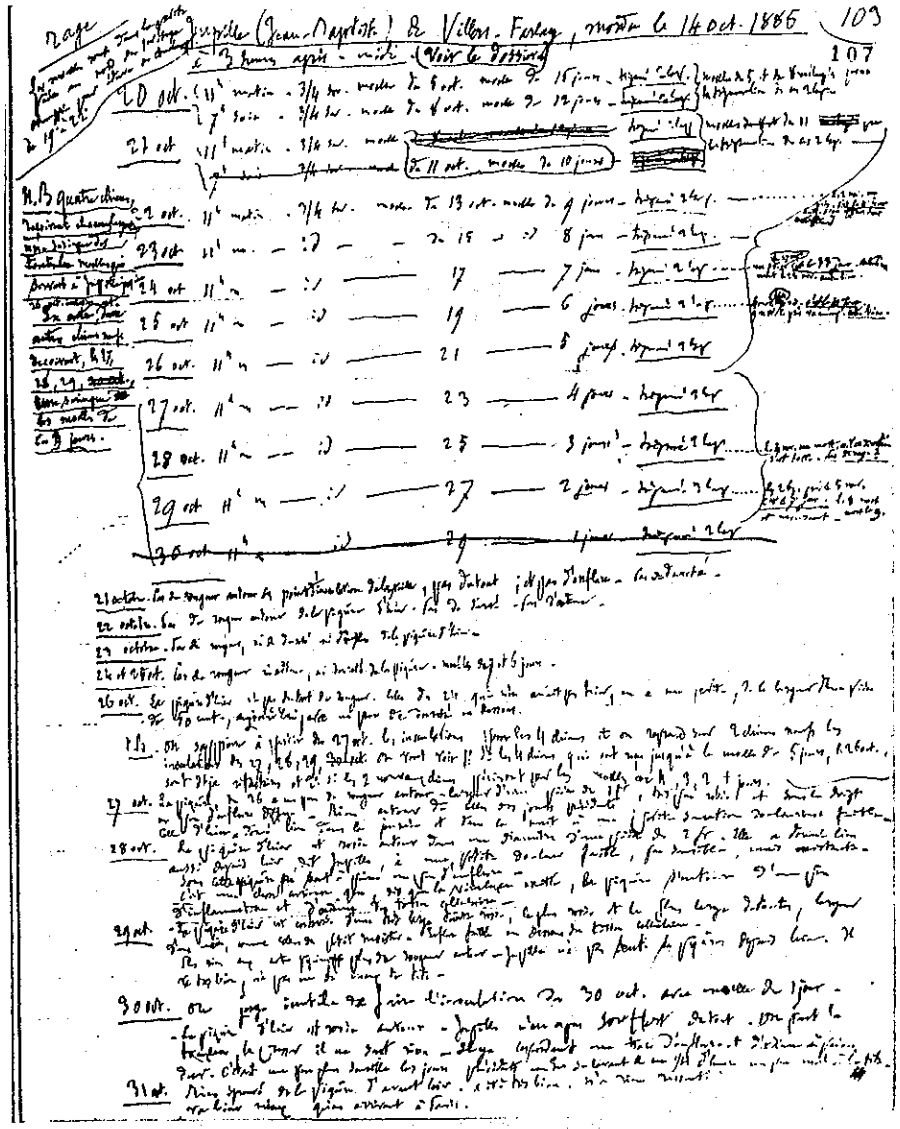


Figure 8.2a.

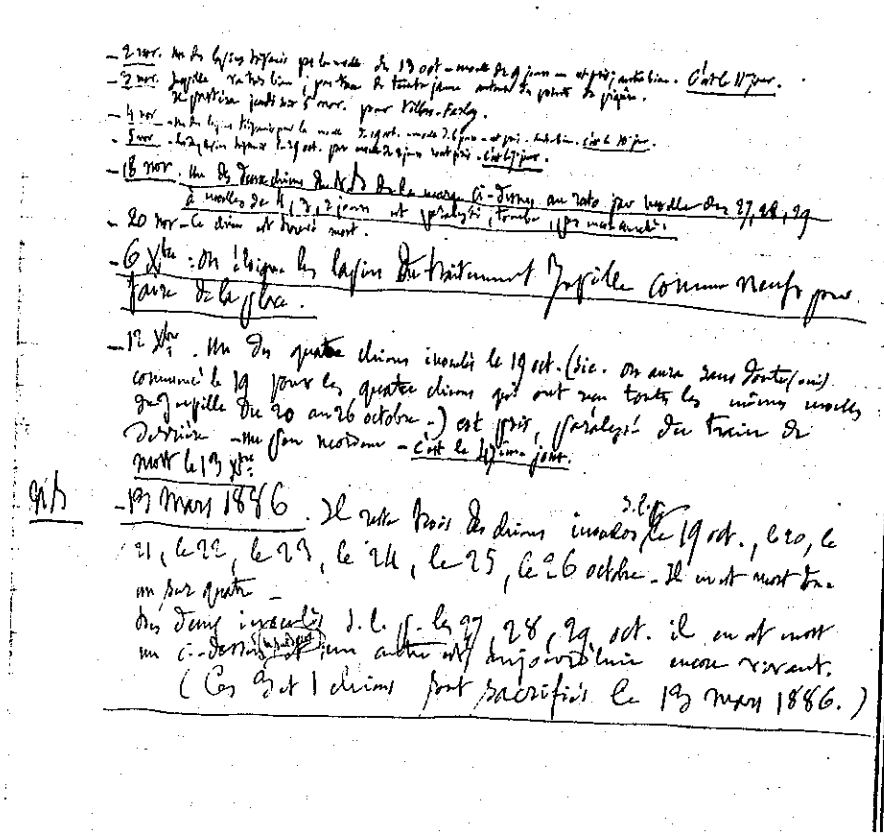


Figure 8.2 (a,b). Pasteur's laboratory notes on the treatment of Jean-Baptiste Jupille, beginning on 20 October 1885. Pasteur, *Cahier 94*, fols. 103–103v (using Pasteur's handwritten pagination). (Papiers Pasteur, Bibliothèque Nationale, Paris)

> As [Jupille] is doubtless not rich, I will keep him with me, in a room in my laboratory. . . . The village will only pay the expenses of his round-trip voyage. I covered all the expenses to which I allude for young Meister [as well]. It is true that I do so in view of these being my very first trials. Later, I think, the municipalities or general councils will be asked to intervene [fiscally].[5]

In his response to this letter from Pasteur, Mayor Perrot reported that he had communicated its contents to Jupille's parents. They had been reluctant at first to send their son off to Paris, having heard conflicting advice from all sides. But the mayor told them that the veterinarians' report on the attacking dog left no doubt that it had been rabid and that "their son was lost unless they accepted the generous offer of M. Pasteur, who alone knew how to save him from the horrible death that threatened him." In the end, Mayor Perrot's counsel prevailed. Having secured parental consent to do so, he put young Jean-Baptiste on the next train to Paris with enough money to cover the expenses of his journey.[6]

The treatment of young Jupille began at 11 A.M. on 20 October 1885. Like Joseph Meister before him, he was to undergo a long series of daily injections of Pasteur's new rabies vaccine.[7] On 26 October, the day on which young Jupille submitted to the eighth injection in the series, Pasteur went to the Académie des sciences to deliver the famous paper in which he announced the application of his rabies vaccine to human cases.

PASTEUR'S FAMOUS PAPER OF 26 OCTOBER 1885

Pasteur began his celebrated paper of 26 October 1885 by reporting that his experiments on rabies had taken an important new turn since his last public communication of 10 August 1884. While insisting that his previously announced method of preventing rabies in dogs—namely, by injecting them with a rabies virus attenuated by serial passage through monkeys—had marked a real advance, Pasteur did now concede that the advance had been "more scientific than practical." This method, he now revealed, led to "various accidents," with the result that "not more than fifteen or sixteen dogs in twenty could be made resistant to rabies with certainty." The method had still other practical defects. It took three or four months to be sure that the injected animals had been rendered immune, and the monkey-attenuated virus could not easily be produced and applied at a moment's notice, thereby limiting its utility in the emergencies faced by the victims of the "casual and unforeseen" bites of rabid animals.[8]

Pasteur and his collaborators had therefore pressed onward in search of another method of prevention that was both more rapid and "capable of giving . . . a state of perfect security in the dog." Until that goal was achieved, wrote Pasteur, "it was impossible to think of making any trial of the method on man." But he had great news to report: "After, I may say, innumerable experiments, I have at last found a method of prophylaxis both practical and rapid, and one that has already proved successful in the dog so constantly in so many cases that I feel confident of its general applicability to all animals and to man himself."[9]

The point of departure for the new method was the technique of serial passages through rabbits via Roux's method of intracranial inoculation, which produced a stable or "fixed" rabies virus of maximum virulence and minimum incubation period for both rabbits and dogs. A series of rabbit-to-rabbit passages begun in November 1882 and continued without interruption in the three intervening years had now reached its ninetieth rabbit. The first rabbit in the series had been infected with the spinal marrow of an ordinary rabid dog by Roux's method of direct inoculation onto the exposed brain. The virus was then passed directly from rabbit to rabbit, always by the method of intracranial inoculation. Over the course of the first forty or fifty passages, the incubation period had declined from about fifteen to seven days, where it still remained in the ninetieth passage, though a slight tendency toward a six-day incubation was beginning to emerge. "Nothing is easier, therefore," wrote Pasteur, "than to have constantly at one's disposal, for considerable lengths of time, a virus of perfect purity and always identical with itself." The technique of serial passages was "virtually the whole secret of the method."[10]

Well, not quite. For Pasteur now revealed an even more crucial feature of his new method of preventing rabies. During the past year, he and his collaborators had developed a new technique for altering the virulence of the rabies virus. Instead of passing the virus through monkeys, they now attenuated it by extracting spinal cords from rabbits dead of the "fixed" rabies virus, cutting them into strips several centimeters long, and then suspending these spinal strips from a thread inside a flask with two cotton-stoppered holes at the top and near the bottom. To extract moisture from the filtered air that circulated through the flasks, Pasteur placed caustic potash inside them (see fig. 8.3). Infected rabbit spinal strips that were suspended in this filtered, desiccated air gradually lost their virulence vis-à-vis dogs, becoming harmless after a period of time that varied somewhat with the thickness of the strips but especially with the ambient temperature. Ordinarily, two weeks sufficed to render the suspended strips harmless to

Figure 8.3. The Roux-Pasteur technique for preserving spinal marrow from a rabid rabbit. (Musée Pasteur, Paris)

dogs. "These points," wrote Pasteur, "constitute the scientific part of the method."[11]

Pasteur then described in some detail the precise manner in which he and his collaborators applied these principles in order to render dogs immune to rabies quickly and surely.

> In a series of flasks, the air inside which is kept dry by dropping pieces of caustic potash into them, suspend every day a portion of fresh spinal marrow taken from a rabbit that has died of rabies of seven-days incubation. Every day also inject under the skin of the dog to be rendered immune a full Pravaz hypodermic syringe of sterilized broth in which a small piece of one of the drying marrows has previously been ground up. Begin with a marrow old enough to make sure that it is not at all virulent. . . . On the succeeding days proceed in the same manner with fresher marrows, and use those of every second day, until finally we inoculate a last and very virulent one that has been drying only one or two days.[12]

By this method, Pasteur reported, he had rendered "fifty dogs of all ages and all races immune to rabies without a single failure" when young Joseph Meister unexpectedly appeared at his laboratory door. He decided, "not without profound anxiety," to apply the method to the apparently doomed boy. At 8 P.M. on 6 July 1885, with Drs. Vulpian and Grancher in attendance, Meister was injected "under a fold made in the skin of the upper right abdomen with one-half Pravaz syringe [i.e., one-half cubic centimeter] of the marrow of a rabbit that died of rabies on June 21st." During the fifteen days from 21 June to 6 July, the rabid spinal marrow had been drying out in one of Pasteur's special flasks. Young Meister submitted to twelve additional injections over the next ten days, always in the abdomen, alternately on the right and left sides, and always one-half Pravaz syringe in amount. On the second and third days, 7 and 8 July, he was injected four times, twice each day, with a broth containing infected spinal cords that had been drying out for fourteen, twelve, eleven, and nine days, respectively. Every succeeding day through 16 July, Meister received one injection each day with a cord that had been drying out for one day less than its predecessor. The last injection was made with the most virulent rabies virus available—that contained in a fresh spinal cord from a rabbit dead of a rabies virus that had been repeatedly passed through rabbits.[13]

If this method seemed dangerous, especially toward the end, Pasteur justified it by pointing to the results of his experiments on "the fifty dogs already mentioned." Once a state of immunity had been achieved, he wrote, increasingly virulent injections were without risk and indeed seemed only

to enhance the level of immunity. And the highly virulent injections that came toward the end of Meister's treatment had another important advantage: they drastically reduced the period of time during which one might fear the eventual appearance of rabies. Given the virulence of the rabid spinal cords deployed toward the end, rabies would doubtless appear quickly, presumably within weeks, or else it would not appear at all. And so, as early as mid-August of 1885, five or six weeks after Meister's treatment had begun, Pasteur felt confident that the young Alsatian lad would escape the effects both of the bites of the rabid dog and of the virulent injections to which he had been exposed during the last several days of his treatment. By 26 October, when Pasteur delivered this famous paper to the Académie des sciences, Meister had been in perfect health for three months and three weeks. It therefore seemed almost certain that the threat of rabies had long since passed in his case.

The human interest of Pasteur's paper then gave way to a theoretical digression about how the results of his new method of preventing rabies might be explained—a crucial issue to which we shall return in the next chapter. Pasteur's paper regained its dramatic tone at the end, as he turned to the story of Jean-Baptiste Jupille. The transition came in the form of the statement that "probably the most anxious question at the moment is that of how much time may be allowed to elapse between the bite and the application of the treatment." In the case of Joseph Meister, this interval had been only two days or so, but "it will certainly be considerably longer in a large number of cases." And as a matter of fact, Pasteur now reported, he had already begun treating just such a case a week ago. In this second attempt to apply his new remedy to human cases, once again "obligingly assisted by MM. Vulpian and Grancher," Pasteur was trying to save a fifteen-year-old boy who had been bitten "in circumstances of peculiar gravity" a full six days before his treatment began. Pasteur continued—and concluded—as follows:

> The Académie [des sciences] will hear, not without some emotion, the story of the deed of bravery and cool-headedness accomplished by the boy whose treatment I took in hand last Tuesday. Jean-Baptiste Jupille is a shepherd boy hailing from Villers-Farlay in the department of the Jura. Seeing a powerful dog with suspicious gait attacking a group of six of his comrades, all younger than himself, he seized his whip and rushed forward to meet the animal. The dog at once caught hold of Jupille by the left hand. There followed a hand-to-hand battle, so to speak, the boy finally throwing the animal down and pinning him to the ground under his knee. Next, with his right hand he forced open the jaws of the beast—all the while sustaining new bites—and, taking the thong of his whip, he tied the muzzle of his enemy and beat him to death with one of his wooden shoes.[14]

As Pasteur sat down, his colleagues at the Académie des sciences rose in applause. Three of them asked for the floor. The first speaker, predictably enough, was Dr. Vulpian, who was not only a member of the French rabies commission but had also participated in the decisions to treat young Meister and Jupille. Vulpian expressed his immense admiration for Pasteur's paper, an admiration that he was convinced would soon be shared "by the entire medical world":

> Rabies, that terrible disease against which all therapeutic efforts have hitherto failed, has finally found its remedy. M. Pasteur, who has had no precursor in this line except himself, has been led by a series of researches pursued without interruption for several years to create a method of treatment by which one may prevent, with certainty, the development of rabies in humans who have recently been bitten by a rabid dog. I say "with certainty" [*à coup sûr*] because, after what I have seen in M. Pasteur's laboratory, I have no doubt as to the constant success of this treatment, when it is put into practice in all its particulars [*dans toute sa teneur*] a few days after a rabid bite.
>
> Given all this, we must now preoccupy ourselves with the organization of a treatment service for rabies by Pasteur's method. It is essential that everyone bitten by a rabid dog should benefit from this great discovery, which puts the finishing touch on the glory of our illustrious colleague and adds the most distinguished luster to our country.[15]

The second speaker, one M. Larrey, was so taken by Pasteur's account of young Jupille's courage that he successfully urged the Académie des sciences to award him a national prize for virtue (*prix de vertu*).[16] Last to speak was the veterinarian Henri Bouley, an erstwhile critic of Pasteur's doctrines who had become a convert a decade ago and who now served both as chairman of the French rabies commission and as president of the Académie des sciences. Bouley predicted that Pasteur's report of his latest achievement, "one of the greatest advances ever accomplished in the domain of medicine," would make the date 26 October 1885 "forever memorable in the history of medicine and forever glorious for French science."[17]

Pasteur's exciting news spread throughout the world with astonishing speed. Already famous for his vaccine against anthrax in sheep, Pasteur now became a full-fledged international hero. Victims of animal bites soon flocked to Paris from near and far, from as far away as Russia to the East and America to the West, to benefit from the new treatment. It won lavish praise from nearly all who submitted to it, and centers for the treatment quickly

spread to other countries. By November 1886, little more than a year after young Joseph Meister first went through the series of injections, Pasteur's treatment had been applied to nearly twenty-five hundred people in Paris alone.[18] From virtually everywhere in the world there also came a flood of monetary contributions, large and small, from emperors and schoolchildren, to support Pasteur's center for rabies treatment. The celebrated Institut Pasteur, built and initially sustained by these private donations, was officially inaugurated in November 1888, just three years after Pasteur announced the application of his rabies vaccine to human cases. A statue in front of the building depicts a pitched battle between a rabid dog and the brave young shepherd Jean-Baptiste Jupille. By the time Pasteur died in 1895, some twenty thousand people had submitted to his rabies treatment at centers throughout the world.[19] And the Institut Pasteur in Paris, designed from the first to be a center for basic research as well as for the treatment of rabies, has loomed large ever since in the history of science and medicine.

This is the familiar and triumphal version of the story. But a fuller, more complicated, and somewhat less heroic version deserves to be told. In fact, this revised account is so different from the usual story that it will occupy the rest of this chapter and all of the next one. Here, too, the most compelling material is drawn from Pasteur's private papers and laboratory notebooks, as will become especially clear in the next chapter. But we can anticipate some of the issues to be addressed there if we first amplify the now faint voices of a neglected set of historical actors: those who dared to criticize Pasteur and his treatment for rabies.

FORGOTTEN CRITICS

From the outset, a few scientists and more than a few physicians insisted that Pasteur's new treatment for rabies was ill-founded in principle and downright dangerous in practice. A separate stream of criticism came from anti-vivisectionists and anti-vaccinationists, who were to be found almost exclusively in England.[20] When noticed at all, such critics have been dismissed as benighted obstacles on the path to scientific and medical progress—precisely the reputation that Pasteur and his allies worked hard to pin on them. In 1889, as English critics became increasingly shrill in opposition to a proposed anti-rabies institution in London, their exasperated compatriot T. H. Huxley sallied forth to excoriate them in his inimitable style:

> But the opposition which, as I see from the English papers, is threatened has really for the most part nothing to do either with M. Pasteur's merits or with the efficacy of his method of treating hydrophobia. It proceeds partly from the fanatics of *laissez faire*, who think it better to rot and die than to be kept whole and lively by State interference, partly from the blind opponents of properly-conducted physiological experimentation, who prefer that men should suffer rather than rabbits or dogs, and partly from those who for other but not less powerful motives hate everything which contributes to prove the value of strictly scientific methods of inquiry in all those questions which affect the welfare of society.[21]

This lovely bit of invective allows us to see just how much was at stake here. For Huxley and other scientistic spokesmen, Pasteur's treatment for rabies offered powerful new evidence of the therapeutic utility of an ascendant "scientific" medicine. More than that, it was a symbolic rallying point in a wider struggle for cultural authority and power—between scientific knowledge and clinical experience in medicine; between "strictly scientific methods of inquiry" and traditional sources of authority "in all those questions which affect the welfare of society"; and even—in the English context—between "state interference" and "laissez faire" in politics writ large.

As "Darwin's bulldog," Huxley had already served on the front lines in one major skirmish in this wider cultural battle. Now, three decades later, he was ready to deploy his polemical talents on behalf of the Pastorian enterprise. Nuance and concession played no part in Huxley's rhetorical strategy. Critics of Pasteur's treatment for rabies were to be lumped together with all the other forces of darkness, and all were to be pushed aside in pursuit of a larger project: to secure the cultural dominion of modern "professional" science. There was no need to pay close attention to the actual content of the critiques directed against Pasteur and his rabies vaccine; it was enough to focus on the dubious motives that allegedly inspired them. The success of this strategy is evident in the story line of all standard histories of bacteriology: Pasteur was right and a master of "scientific method"; his critics were not only wrong but also incompetent and desperate defenders of a fading cultural regime.

In France, the Pastorian juggernaut was fueled partly by nationalism. We have already heard from Pasteur's colleagues at the Académie des sciences, where it was said that his rabies vaccine "adds the most distinguished luster to our country" and that the date of its announcement, 26 October 1885, would be "forever glorious for French science." Not for the first time, nor for the last, Pasteur and his allies appealed to French national pride in support of his research. Pasteur himself had already called the germ theory of

fermentation a "French" discovery, and he insisted that any beers that might be manufactured under his patents should be called "bières françaises" for domestic consumption and "bières de la revanche nationale" abroad. He also wrote that he would have been "inconsolable" had experimental vaccination been anything but "a French discovery."[22]

Anti-Pastorian sentiment did exist, even in France, but it was confined mainly to the "popular," leftist or anti-establishment press.[23] In "official" French circles—the Académie des sciences and the Académie de médecine, in both of which Pasteur was an honored member—the Pastorian treatment for rabies went almost unchallenged. The only notable or, rather, notorious exception was the clinician Dr. Michel Peter, a member of the Académie de médecine, about whom we shall soon hear a good deal more. By 1887, another quixotic French critic of the new rabies vaccine, Dr. Auguste Lutaud, was thoroughly frustrated by the Pastorian success at playing the nationalist card. In France, wrote Lutaud, "One can be an anarchist, a communist, or a nihilist, but not an anti-Pastorian; a simple question of science has been made into a question of patriotism."[24]

For the most part, Pasteur was lucky in his critics, both at home and abroad. Few in number and ineffectual in strategy, they were quickly overwhelmed by the Pastorian forces. They did their cause no favor by adopting a strident, hectoring tone that betrayed their personal hostility toward Pasteur. The clinicians among them were too obviously self-serving when they complained about the intrusion of this "mere chemist" into their traditional domain. By the late 1880s it was no longer enough simply to assert, as these doctors did, that the proper foundation of medicine was clinical experience, not animal experiments—that medicine was an "art," not a science.

And yet, for all of that, these few and forgotten critics did sometimes hit a raw Pastorian nerve, and some of their objections were more telling than the public record suggests. Even as they went down to defeat, these critics caused Pasteur some real concern and embarrassment, almost all of it hidden from public view. The critiques can be divided into three broad categories, as indeed they were at the time:[25] (1) *experimental or "strictly scientific" issues*—most obviously when experiments elsewhere did not fully confirm Pasteur's results, but also when the participants could not agree about what counted as a properly "scientific" approach to the issues in dispute; (2) *clinical concerns*—including the challenge of diagnosing rabies, especially in patients who displayed nervous symptoms after having been bitten by rabid animals and then submitting to Pasteur's "prophylactic" treatment; and (3) *statistical arguments*, perhaps the most disputatious arena of all. Actually, we can add a fourth, still broader category of dispute, which implicitly links the other three: *ethical concerns* about Pasteur's conduct and about the safety and efficacy of his treatment.

THE 1887 DEBATES IN THE ACADÉMIE DE MÉDECINE OVER PASTEUR'S WORK ON RABIES

We need not cast our net very widely to capture the specific issues in dispute under these broad categories. They were conveniently brought together in a series of heated debates at the Académie de médecine between January and July 1887.[26] Perhaps the word "debates" is a bit misleading here, for the deck was heavily stacked in Pasteur's favor. Indeed, one of the most striking features of the controversy, as recorded in the *Bulletin* of the Académie de médecine, is how completely it overturns the widespread notion that Pasteur had to battle fiercely against a conservative medical establishment. For in fact, almost all members of the Académie de médecine were openly enthusiastic about Pasteur's work on rabies and his vaccine against it.

Pasteur's critics, in striking contrast, were represented by one lonely voice in the Académie de médecine: Dr. Michel Peter, who was in fact Pasteur's cousin-by-marriage, a relationship that may have given him access to "insider information" from members of the tight-knit Pastorian inner circle.[27] An elegant man of the world and a clinician of the old school, Dr. Peter was responsible for instigating and prolonging the debates. He was in some ways the worst possible spokesman for Pasteur's critics. He wasted too much time on anecdotal "case histories" of patients who had allegedly died of rabies after submitting to Pasteur's treatment. His arguments quickly became repetitive and tiresome. And his relentlessly hostile and accusatory tone toward Pasteur won him no friends in the Académie de médecine or anywhere else in the French medical and scientific establishment.

During the debates at the Académie de médecine, Peter was not merely outnumbered and outwitted, he was also outmaneuvered and even hissed and booed. The president and the perpetual secretary of the Académie clearly arranged things in Pasteur's favor,[28] and we can be virtual witnesses of the general audience response thanks to the Académie's charming practice of including crowd noises as part of the published account of its meetings. From the account published in the *Bulletin* of the Académie de médecine it is clear that its members greeted Pasteur and his many defenders with respect and applause, while Peter's disquisitions were punctuated with muttering and hissing, with nary a single recorded indication of applause.[29] At the last debate, on 12 July 1887, when Charcot as president gave a ringing and concluding defense of Pasteur and his work, the audience responded with "prolonged applause."[30] By then, Dr. Peter must have felt disheartened and even beleaguered. He was certainly defeated, indeed overwhelmed, like so many other would-be critics of Pasteur.

Insofar as Dr. Peter's campaign against Pasteur did attract any attention outside the Académie de médecine, it was mainly because several people had recently died of rabies after undergoing Pasteur's treatment. Much of the debate, especially at first, concerned the particular circumstances surrounding these deaths and their implications for the safety and efficacy of Pasteur's vaccine. At one point, Dr. Peter went so far as to accuse Pasteur of direct responsibility for at least one such death. Dr. Vulpian expressed his sense of the gravity, if not the accuracy, of Peter's assertions by saying that they amounted to a charge of "involuntary homicide" against Pasteur.[31]

Dr. Peter's reckless accusations infuriated most members of the Académie de médecine and doubtless most of France and the international scientific community as well. Such rhetorical disasters undermined Peter's more general and sometimes more telling case against Pasteur's work on rabies, which attracted little attention at the time and has been almost entirely ignored in the century since. Yet Peter's critique, however overwrought and ill-advised in tone, included some intriguing challenges to Pasteur's work on rabies. It covered the full range of experimental, clinical, statistical, and ethical issues. And even some of Peter's most outrageous accusations were not entirely unfounded, as will become clear in the next chapter.

When it came to experimental issues, Dr. Peter had to rely on the work of others, for he had no experience or credentials of his own in experimental research, as Pasteur was quick to point out in his disdainful replies to Peter's attacks. Yet Dr. Peter displayed no great concern about his experimental "incompetence," saying that it put him in the good company of 99 percent of the members of the Académie de médecine.[32] More important, Peter's own experimental expertise was not at issue here. How, he asked in effect, did Pasteur propose to refute the serious experimental critiques published by more competent scientists? In a surprisingly clever move, Peter made the question more pointed by drawing special attention to the independent critiques produced by two scientists—one from Italy, the other from Austria—who had come to Pasteur's own laboratory in Paris to learn his techniques at first hand, only to find that they were unable to replicate the Pastorian results upon their return to their native laboratories. In particular, they were often unable to prevent rabies in experimental animals outside of France, even when they began with emigré French-born laboratory animals given them by Pasteur himself and tried to follow Pasteur-perfect techniques.

Here Dr. Peter unwittingly displayed his prescience as a sociologist of knowledge. A century ago, he taunted Pasteur as if already aware of the contingencies of experimental knowledge—as if he already knew how hard it was to translate "local knowledge" from one experimental setting to another, no matter how carefully scientists at other sites tried to imitate the technical gestures of the original laboratory, including here even the "same" laboratory animals. But Dr. Peter was, of course, "ahead of his time," and Pasteur knew how to deal with such cultural precocity—if only because he was himself the best sociologist of knowledge around, as Bruno Latour has been trying to persuade us for years.[33]

Even so, Pasteur had to recover from a sort of philosophical or sociological *faux pas*, though he was pushed before he slipped. Under pressure, he had laid himself open to "the replicability problem." The pressure came in the form of renewed complaints about his secrecy—complaints that echoed those voiced five years earlier during his research on the anthrax vaccine, as we have seen in the story of the "secret of Pouilly-le-Fort." This time Pasteur decided to meet the complaints head on. He allowed outsiders, strangers, even foreigners, to observe the Pastorian techniques for preventing rabies on the spot, behind the usually closed doors of his laboratory. He did so, it seems, with complete confidence that all of these outsiders would go away convinced of the merits of his treatment for rabies. He was mistaken, and oddly so for such a sophisticated sociologist of knowledge.

In a letter of 22 July 1886, Pasteur told the vice-president of the Municipal Council of Paris that he could easily refute "the odious falsehood" that "*Pasteur keeps his method secret.*" For not only were there Frenchmen "who know all the details of [my] method" of preventing rabies, there were also a number of "foreign doctors" who had studied the method in his laboratory, some of whom had "already founded institutes to apply it in their respective countries." And far from keeping his method secret from these foreign doctors, he had even given some of them the "initial material for [their] inoculations." He listed eight such foreign visitors, who had come to his laboratory from as far away as Odessa to the east and New York City to the west.[34]

But at least two foreign doctors were soon to give Pasteur cause to regret his hospitality to them: Dr. Amoroso of the First Medical Clinic at the University of Naples, and Professor Anton von Frisch of Vienna. Dr. Peter cited both of them as part of his attack on Pasteur at the Académie de médecine in 1887. Amoroso published at least two brief critiques of Pasteur's method of preventing rabies. He reported that he had been unable to replicate all of Pasteur's results despite having studied the Pastorian techniques for three weeks in Paris, and despite having begun with two rabid animals that Pasteur himself had given him to take back to his laboratory in Naples. Amoroso's experiments on rabbits, guinea pigs, and dogs led him to two conclusions, of which the first was entirely in keeping with Pastorian results: rabies was invariably transmitted from one animal to another by Roux's method of intracranial inoculation. But it was Amoroso's second conclusion

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that Dr. Peter was eager to announce: that Pasteur's method of treating rabies was totally ineffectual in animals that had been inoculated with the virus by Roux's method. In response, Pasteur and his allies resorted to the petty complaint that Dr. Amoroso had inflated his credentials by calling himself "professor," and otherwise discredited his two brief critiques.[35]

Professor von Frisch of Vienna was less easily dismissed. In 1887 von Frisch published an extensive and impressively detailed critique of the Pastorian treatment for rabies in a book that covered more pages than the entire corpus of Pasteur's published papers on the subject: *Die Behandlung der Wuthkrankheit: Eine experimentelle Kritic des Pasteur'schen Verfahrens* (*The Treatment of Rabies: An Experimental Critique of the Pastorian Techniques*).[36] The book appeared just in time for Dr. Peter to enlist von Frisch as a witness for the prosecution, so to speak. Because von Frisch's scientific credentials were solid, and because his critique was so extensive, Pasteur privately expressed considerable concern and irritation in the face of this challenge.[37] For current purposes, we need not give von Frisch's critique the full analysis it deserves. We will confine attention here to its fate in the debates at the Académie de médecine.

Von Frisch's critique ranged widely. It included discussions on the clinical and statistical issues in dispute. In these domains, von Frisch did not have anything strikingly original to say, although he was an insightful critic of the Pastorian statistics, which he called "totally worthless," mainly because there was reason to doubt that the Pastorians had kept their vow to treat only people who had been seriously bitten by a certifiably rabid animal.[38] But the centerpiece of von Frisch's critique was his experimental case against the Pastorian vaccine. Von Frisch, it deserves repeating, was one of the few scientists outside Pasteur's inner circle who had been allowed to observe at first hand the way in which the Pastorian team actually went about its day-to-day work on rabies. Yet despite the crucial "craft knowledge" he had thus obtained, von Frisch reported that he had been unable to replicate the apparently decisive results claimed by the Pastorians. Perhaps most disconcertingly to the Pastorians, he insisted that he—like Dr. Amoroso—had been unable to prevent rabies in dogs that had been inoculated with the rabies virus by Roux's intracranial method.[39]

In responding to von Frisch's critique, Pasteur resorted to a familiar ploy: he expressed doubts about the Austrian's technical competence, suggesting that von Frisch lacked the skill to achieve sterile conditions in his experiments and insisting that he had made a fundamental mistake by using dogs instead of rabbits in his attempts to produce a rabies vaccine. Von Frisch responded with understandable outrage at Pasteur's ad hominem attack:

Who says I'm incompetent? Only Pasteur. And Pasteur says he is opposing his positive results to my negative findings. But who is defining "positive" and "negative" here? Once again, only Pasteur, who defines as "positive" those experiments that support his vaccine and "negative" those that do not.[40] Like Pouchet before him in the spontaneous generation debate, von Frisch was objecting to Pasteur's high-handed way of *defining* a priori which experimental results were to count and which were not.[41]

And like Pouchet before him, von Frisch lost the debate, at least in France. Nor was von Frisch, any more than Pouchet, unjustly robbed of a victory that clearly should have belonged to him. Pasteur and the Pastorians were very effective. In public, they kept their composure. And in defending himself against von Frisch and other critics, Pasteur made exceptionally clever use of another wide-ranging analysis of his work on rabies: the Report of the English Commission on Rabies, also published in 1887 and therefore available for use in the debates at the Académie de médecine.[42] In fact, no more judicious assessment of Pasteur's method of treatment appeared during his lifetime. The English commission report was solomonic in its judgments. It expressed admiration for Pasteur's experiments, some of which the commission had repeated successfully—conducted, it deserves emphasizing, under Pasteur's close supervision.[43] The report also expressed the belief that Pasteur's new treatment for rabies had probably saved many lives.

But the English commission also drew attention to the uncertainty of all statistics on rabies, citing the difficulty of establishing that the attacking animal had in fact been rabid as well as the variable effects of the location and depth of bites, of differences in the lethality of rabid animal bites in different species and races, and of the possible prophylactic effects of cauterization or other treatments applied to bitten victims before they submitted to Pasteur's treatment. The commission also suspected that at least one man may have died as a direct result of the Pastorian injections, and in the end it favored strict regulations on potentially rabid animals (muzzling and quarantine) over Pasteur's more drastic remedy.[44] Indeed, such "police" measures were already operating with striking success in Australia and Germany. And though many English pet lovers objected to such state interference, especially to laws that required them to muzzle their dogs, the eventual adoption of such measures in England virtually eliminated rabies there by the turn of the century.[45]

Despite these reservations, Pasteur seized on the Report of the English Commission on Rabies as a weapon in his battle with Dr. Peter (and his outside foreign experts). He managed to make it sound like a ringing endorsement of all his work on rabies,[46] and Peter proved unable to take

advantage of the less positive parts of the Report. So the English rabies commission, presumably unbiased, helped the Pastorians to push aside yet another set of critics. In the end, as we have already seen, Pasteur carried the day in the 1887 debates at the Académie de médecine, overwhelmingly so. But his victory was due not so much to any decisive experimental evidence nor even to the endorsement of the English commission. It was rather a testament to his hard-earned scientific authority and rhetorical skills, and—not least—to a rapidly mounting body of statistical evidence that seemed clearly to show the safety and efficacy of the Pastorian vaccine in human cases.

In a way, it is a shame that Pasteur's victory in the 1887 debates was so overwhelming. For that outcome obscured some interesting and important issues that were lurking just beneath the surface of the debates—and once or twice surfaced in Peter's otherwisé hapless attacks. In particular, Peter struggled unsuccessfully to draw Pasteur and his allies into a quasi-philosophical discussion as to whether or not Pasteur's work on rabies was truly "scientific" and, more important, ethical.[47]

Peter, of course, insisted that Pasteur's rabies vaccine was not truly "scientific" and that it was unethical to boot. He argued, first of all, that Pasteur's work on rabies was not properly scientific because he kept the details of his experiments secret. Like all purveyers of "secret remedies," Peter charged, Pasteur said both too much and too little about his treatment for rabies—enough to attract fame and funds, but too little to allow independent evaluation or replication of his claims.[48] Here Dr. Peter was echoing complaints about Pasteur's secrecy that had already surfaced in the Académie de médecine seven years before, during the debate over his work on anthrax and "the secret of Pouilly-le-Fort," as discussed in detail in Chapter Six. At that time, Roux had warned Pasteur that many physicians, in particular, considered his laboratory an improperly "secret sanctuary." And now, in 1887, Pasteur's early accounts of his work on rabies, through their reticence about the details of his experiments and his techniques for producing the vaccine, invited similar complaints.

To all such charges, Pasteur responded by insisting on the need for careful quality control and by denying that his motives were in any way mercenary. He pointed to the risk of a fatal disaster if the details of his method became known to those less experienced than he and his collaborators, and he reminded his critics that he dispensed his rabies treatment for free. He also emphasized, as we have already seen, that he had revealed the details of his techniques to dozens of scientists, including several foreigners who came to his laboratory to learn those practices on the spot.[49]

Even so, Dr. Peter complained, Pasteur's vaccine against rabies could not be considered properly scientific because it lacked any theoretical foundation. Pasteur was famous for his germ theory of disease, but he had failed to isolate or cultivate the microbe allegedly responsible for rabies. In developing his other vaccines, all for animal diseases, Pasteur had cultivated an attenuated strain of the specific microbe to which he ascribed each disease. But his rabies vaccine had been obtained by mere "empirical" manipulations of rabid spinal cords. For Dr. Peter, Pasteur's research on rabies represented nothing but "empiricism embellished by contradiction." He accused Pasteur of yielding to a "deceiving induction" in extending his experiments from rabbits to dogs and then from dogs to humans. And if Pasteur's original method of vaccination was "scientific," he hinted darkly, why had he modified it more than once since treating Joseph Meister in July 1885?[50]

In their responses to such criticism, Pasteur and his allies took advantage of a confusion that is still very much with us—the confusion between that which works, that which is true, and that which is scientific. One of Pasteur's supporters, the distinguished Dr. Brouardel, offered this blatantly utilitarian defense of the treatment:

> As to the reproach directed against the method as being anti-scientific, I avow that I do not understand it. . . . In my opinion, that alone is anti-scientific which is not true. If someone demonstrated to me that rabies could be cured by the use of a fantastic omelette or oyster-shells, I would still find the thing scientific. In the end, those who seek this quarrel with Pasteur simply ask him the how and the why of the method. M. Pasteur will tell us that when we have found the answer to the question posed by our great comic [Molière]: why does opium produce sleep?[51]

Early on in the debate, Pasteur himself blandly asserted that the "scientific basis" of his treatment lay in "the possibility of conferring immunity against the virus of street rabies in animals by the sub-cutaneous injection of increasingly virulent rabbit spinal cords."[52] But this was merely to transform a raw empirical result into a "scientific" foundation for his treatment. Peter was asking for more. But Pasteur, whose work on rabies was indeed more "empirical" than usual for him—though far less so than his unsuccessful efforts to improve the quality of French beer—displayed no interest in Peter's quasi-philosophical concerns. He and his allies deflected attention from this and other concerns by pointing to the overwhelmingly favorable statistics that Pasteur could marshall on behalf of his vaccine. In particular, the Pastorians emphasized that the mortality rate after his treatment was less than one percent, compared to 15 to 20 percent for untreated victims of rabid dog bites. What more could one ask?

Although Pasteur displayed no public concern about the matter, he did find it somewhat harder to shrug off Dr. Peter's charge that the application of his new vaccine to human cases was not only unscientific, but also, and more importantly, unethical. One ethical concern was based on a simple but fundamental feature of Pasteur's vaccines that he had himself done much to emphasize. Unlike the vaccine against smallpox that Jenner had taken from nature almost a century ago (in the form of cowpox), Pasteur's vaccines against rabies and other diseases were products of the laboratory. Pasteur was proud of this difference between Jenner's vaccine and those he and his collaborators had produced against chicken cholera, anthrax, swine fever, and now rabies. As products of the laboratory, Pasteur insisted, his vaccines were more susceptible to human manipulation and control than Jenner's smallpox vaccine.[53]

But a few critics, notably Drs. Peter and Lutaud, were quick to point out that Pasteur's "artificial" viruses might be the source of a novel disease of Pasteur's own making—*artificial or laboratory rabies* or even *la rage Pastorian*. Like current critics of recombinant DNA research or other forms of "genetic engineering," Drs. Peter and Lutaud expressed concern that Pasteur's treatment made use of altered rabies viruses of uncertain and potentially lethal properties. As evidence that this fear had some basis in reality, Dr. Peter and others pointed to the frequency with which the paralytic form of rabies seemed to appear in those who submitted to Pasteur's vaccine, as opposed to its rarity under natural conditions.[54]

Dr. Peter was especially alarmed by the dangers of the modified "intensive" method of treatment that Pasteur had introduced for certain cases, especially for victims of severe wolf bites or those who came for treatment only a long time after they had been bitten by a rabid animal. Pasteur's "intensive" method involved earlier and more frequent injections of virulent spinal cords, and Peter considered it reckless and wholly unjustified. He and other clinicians also complained that Pasteur's use of "live" (if inactivated) rabies viruses complicated the uncertainties of diagnosing rabies in any vaccinated person who later developed a nervous disorder of uncertain origin and character. And despite the glowing statistics that Pasteur cited in support of his vaccine, a small but steady trickle of people did become paralytic or even died after submitting to the treatment.[55]

At first sight, all such clinical objections to Pasteur's rabies vaccine seem ludicrous in view of its overwhelming statistical success. Surely a few difficulties, complications, and even deaths were inevitable upon the introduction of any novel treatment for a lethal disease. Surely Dr. Peter and his allies were demanding that Pasteur's rabies vaccine meet unreasonably high

standards of uniformity, reliability, safety, and efficacy.[56] And surely Dr. Peter would have resisted the application of such exalted standards to the ordinary therapeutic measures that he and his fellow clinicians deployed every day.

But Peter could respond by insisting that rabies posed very special ethical problems. This is not to say that Peter's concerns found explicit expression in the formal language of current "bioethics." But he and others—including indeed Pasteur himself—recognized that rabies and Pasteur's vaccine against it posed a unique ethical dilemma. In fact, rabies is unlike any other disease on earth, and ethical postures appropriate to less peculiar maladies are not always equally appropriate to it. In this chapter, we will focus on those timeless features of rabies that raise a special ethical dilemma for *any* attempt to treat it. And we will end by noting Pasteur's own stated position about these ethical issues up to the point at which he decided to apply his vaccine to young Joseph Meister.

THE TIMELESS ETHICAL DILEMMAS RAISED BY RABIES

Rabies is, of course, a horrible and invariably fatal disease. As of 1977, the U.S. Center for Disease Control had recorded only three cases of presumed recovery from symptomatic rabies in all of human history.[57] But it is also very rare in humans, at least in the industrialized world. Moreover, rabies is not a "communicable" disease in the usual sense; it is not transmitted from person to person. As a rare and noncommunicable disease, rabies has never seemed to justify the risks or the intrusion on individual rights that compulsory vaccination against any disease entails. Vaccination against rabies makes sense only in the case of very small and well-defined populations—namely, those who are exposed to an exceptionally high risk of contracting the disease either because they work in a rabies-saturated environment (for example, in laboratories conducting research on the disease) or, much more usually, those who have already been bitten by a certifiably rabid animal. Ordinary preventive measures, including vaccines against smallpox, polio, and other infectious diseases, can be encouraged and justified on the grounds of their potential benefit to society at large as well as the individual submitting to them. Rabies vaccination, by contrast, can be justified solely on the basis of its potential benefit to the vaccinated person, who poses no threat to others.

But if Pasteur's vaccine was therefore unlike ordinary preventive measures, so too was it unlike ordinary therapeutic measures. For even in the

case of a person already bitten, the situation is far from straightforward. In the first place, it is sometimes impossible to capture the attacking animal and establish that it was indeed rabid. More important, there is no way to be sure that even the bites of a certifiably rabid animal will lead to rabies in the victim. In fact, the level of uncertainty is high. The mortality rate of "declared" or symptomatic rabies is effectively 100 percent, but the threat of death from the bites of a rabid animal is vastly less. Depending on such factors as the species of attacking animal (wolf and cat bites, for example, seem to pose a much higher risk than dog bites), the depth and location of the bites (bites on the face are much more lethal than those on the hands or limbs), and the application and timing of cauterization or other treatments for the bites, estimates of the risk of contracting rabies from the bites of a certifiably rabid animal range from as high as 60 percent to as low as 5 percent. It is perhaps futile to try to settle on a meaningful "average" figure within this wide range, but it is worth emphasizing that Pasteur himself estimated that only 15 to 20 percent of people bitten by rabid dogs would eventually die of rabies if they would not or could not submit to his treatment.[58]

In short, the great majority of the victims of rabid animal bites could forgo Pasteur's treatment without experiencing any untoward consequences in the future. And they had to decide whether or not to submit to the treatment at a point when they had no symptoms of the disease. For the efficacy and very possibility of Pasteur's vaccine depended on the peculiarly long incubation period that separates the infective bites of a rabid animal from the outbreak of symptoms. At some point during this incubation period, perhaps as soon as a week or two, the vaccine loses its capacity to prevent the disease from taking its natural and invariably fatal course. Once the symptoms become manifest, neither Pasteur's vaccine nor any other is of any use. But those who choose to undergo the series of vaccinal injections have no way of knowing whether or not they would ever have fallen victim to rabies had they made the opposite decision. There is simply no way to be sure that the rabies vaccine is even potentially beneficial to the vaccinated individual. In this crucial respect, Pasteur's "treatment" was unlike ordinary therapeutic measures, undertaken for the immediate sake of a person already suffering from a disease. When he vaccinated asymptomatic victims of animal bites, Pasteur was subjecting them to a painful and inherently risky series of injections even as he knew that many and probably most of them would escape the disease anyhow.

Not even AIDS, the only other human disease with a mortality rate of 100 percent (or so we believe thus far), poses such a unique ethical dilemma.

True, the symptoms of full-blown AIDS, like those of rabies, appear only after a long incubation period of the implicated virus (HIV)—a similarity that explains why several teams of investigators are now in frantic pursuit of a safe and effective "postexposure" vaccine against AIDS. Pasteur's treatment for rabies, like all its successors, was also based on "postexposure" vaccines. But in the case of AIDS, one can predict the eventual emergence of the disease with a high, if imperfect, degree of confidence because the HIV virus can be detected in the blood. In striking contrast, Pasteur had no secure way of knowing that asymptomatic victims of rabid animal bites had been infected with the rabies virus. In effect, every decision to treat an asymptomatic victim of rabid animal bites entails an exquisite "moral calculus," in which a low probability of infection must be balanced against a 100 percent fatality rate once the symptoms appear.

If these distinctions now seem overly precious, that is only because the accumulated statistical evidence of a century suggests that the risk of death or serious harm from rabies vaccination is much less than the risk of death from the bite of rabid animal. True, there have always been thoughtful critics of this superficially convincing statistical evidence for Pasteur's vaccine,[59] and even the Pastorians themselves became concerned about the persistent if rare "accidents" (paralysis or death) that followed the treatment. Indeed, by the time Pasteur died in 1895, the Institut Pasteur itself had switched from his original "live" vaccine to an inactivated carbolic acid vaccine, and the rabies vaccines developed since differ even more radically from Pasteur's initial version.[60] Even so, as the statistical evidence available to Pasteur seemed increasingly to justify his vaccine, he was able to claim a sort of retrospective ethical sanction for it.

But the situation was entirely different when Pasteur first applied his treatment to young Joseph Meister. At that point, obviously, there was no "statistical" evidence of the safety and efficacy of his vaccine. Three months earlier, as described in the previous chapter, Pasteur undertook his secret attempts to cure M. Girard and Julie-Antoinette Poughon of symptomatic rabies. In their case, however, he faced a much less difficult ethical dilemma. For he was then undertaking a clearly *therapeutic* trial on two patients whom he had every reason to believe would otherwise face certain death. But when Pasteur decided to treat the asymptomatic Joseph Meister, he was conducting an experimental trial of a "live" rabies vaccine on a human "subject" who had some real if indeterminate chance of surviving without it—an unusually risky form of human experimentation in which there was no fully secure way of knowing whether the trial was even potentially of benefit to the individual submitting to it.

PASTEUR ON THE ETHICAL ISSUES RAISED BY RABIES

From the outset of his quest for a rabies vaccine, Pasteur clearly appreciated the problems posed by the ethical strictures against nontherapeutic human experimentation. More than once, he addressed the issue explicitly. On 15 May 1884, for example, he told an audience from the Friendly Association of Former Students of the Ecole Centrale des Arts et Manufactures that he and his collaborators had managed to produce an attenuated strain of the rabies virus—in a word, a vaccine—that was yielding very promising results in tests on dogs, and he held out the prospect that such a vaccine might soon be applied to humans. He also reported that increasing public awareness of his quest for a rabies vaccine had already brought him numerous requests for treatment from anxious victims of animal bites; he would doubtless receive many more such appeals in the future. But, he insisted, any clinical trial of a rabies vaccine would perforce pose ethical concerns about human experimentation. First, he would need to secure the aid of a physician, since he did not possess an M.D. degree. He would ask a doctor to join him in any human trials "so as not to engage in illegal medical practice." More important, Pasteur emphasized that he would undertake such trials only after extensive and decisive experiments on animals. Not only would he need first to "acquire the certainty of being able to prevent the disease in dogs"; he would also forgo any human trials until "after having multiplied the same proofs in animals, on dogs, monkeys, and particularly on the bovine species, which seems to contract rabies as a result of bites much more easily than man or the dog."[61]

In August 1884 he delivered a similar message to the International Medical Congress in Copenhagen. He told his audience that he had undertaken the study of rabies precisely because it offered the possibility of a way around the accepted precept that "experimentation, while allowable in animals, is criminal in man." Rabies was the most striking example of an invariably lethal disease common to man and animals, and prior experiments on animals could therefore be used to establish the safety and efficacy of a rabies vaccine before it was applied to human cases. But even then, "proofs must be multiplied *ad infinitum* on diverse animal species before human therapeutics should dare to try this mode of prophylaxis on man himself."[62] And as late as December 1884, Pasteur resisted a written plea to treat a bitten child because his method had not yet been securely established in the case of dogs already bitten. Even should he be able to achieve that goal, wrote Pasteur in his response to this plea, his hand would "tremble" before applying the treatment to humans, "for what is possible in the dog may not be so in man."[63] As late as 12 June 1885 he declined to treat a bitten father and his child on the grounds that his researches had not yet reached the point that would allow him to apply it to man.[64]

Yet a mere three weeks later, on 6 July 1885, Pasteur made the opposite decision in the case of young Joseph Meister, with the happy outcome now known to all. What had happened in the meantime to change Pasteur's mind? Had he achieved his goal of "multiple proofs from diverse animal species" as to the safety and efficacy of his rabies vaccine? Put another way, had he met his own criteria for an ethical human trial of his treatment?

NINE

Private Doubts and Ethical Dilemmas: Pasteur, Roux, and the Early Human Trials of Pasteur's Rabies Vaccine

ONE DAY in the mid-1880s, the "independent" research of Pasteur and his leading collaborator on rabies, Emile Roux, came too close for comfort. On that day, or so we are told by Pasteur's nephew and research assistant Adrien Loir, he prepared some cultures of the swine fever microbe, working as always under Pasteur's watchful eye, and carried them to a laboratory stove. Since Loir's hands were filled with flasks, Pasteur opened the door of the stove for him. As Loir went about his usual tasks, Pasteur noticed an unusual flask in the stove: a flask of 150 cubic centimeters supplied with two tubules open to the ambient atmosphere, one above the other and so arranged as to produce a continuous stream of ordinary air inside the flask (see fig. 8.3). Loir's account continues as follows:

> In this flask a strip of rabbit spinal cord was suspended by a thread. The sight of this flask, which [Pasteur] held aloft, seemed to absorb [him] so much that I did not want to disturb him. . . . After a long silence, he asked me, "Who put this flask here?" I answered that "it could only be M. Roux," for "this is his rack." [Pasteur] took the flask and went down the hall. He raised it above his head, and set himself to look at it in the full light of day for a long, long time. Then he returned to put the flask back in its place [on Roux's rack in the stove] without saying a word.[1]

But if Pasteur said little to Loir about Roux's unusual flask, he did immediately order the construction of a dozen similar flasks—stipulating, however, that they should differ from Roux's flask in two ways: they should be much larger in volume, and they should contain caustic potash in order to

dry the air flowing through them. By adding caustic potash, which Roux had not done, Pasteur hoped to prevent the spinal strip from putrefying in ordinary air. Under those conditions, any attenuation of the rabies virus in the spinal strip could be ascribed to the effect of "allowing [atmospheric] oxygen time to attenuate the virus"—in keeping with Pasteur's preference for oxygen-attenuated vaccines.[2]

The very next day Pasteur began suspending strips of rabbit spinal cord in his new desiccating flasks, which he let stand at ordinary room temperature instead of depositing them in the stove, as Roux had done. That afternoon, Roux noticed three of these new flasks sitting on a table in the laboratory. He sent for Loir:

> "Who put those three flasks there," he asked me while pointing to the table. "M. Pasteur," I answered. "He went to the stove?" [asked Roux]. "Yes" [I replied]. Without saying another word, Roux put on his hat, went down the stairs, and left by the door on the rue d'Ulm, slamming it shut as he [always] did when angry.[3]

According to Loir, Roux never said a word to Pasteur about this incident. But thereafter, he claimed, Roux came to the laboratory only at night, when he knew he would not cross paths with Pasteur. And from that moment, Loir continued, rabies became a "dead letter" for Roux.[4]

Here, as often elsewhere in his reminiscences, Loir provides no exact date—not even a year—for this anecdote. But Loir surely did not intend his last sentence to be taken literally. For Roux did not become permanently estranged from the Pastorian rabies project. Elsewhere, Loir himself describes Roux's return to Pasteur's laboratory and his crucial contributions to its work on rabies. Even so, Loir's anecdote is a striking illustration of a more general theme: the tension between Pasteur and Roux. The exact nature of the relationship between them has long been an object of discussion and speculation. To judge from the most credible accounts, this was not a simple case of an affectionate disciple working happily under the master's yoke.[5]

From time to time in the rest of this chapter, I will suggest that at least some of the discord between Pasteur and Roux over rabies can be traced to differences in their professional formation and orientation. Here Pasteur as life-long experimental scientist is contrasted with Roux as a former medical man who never forgot the lessons of his brief career in clinical medicine and who carried part of that professional ethos with him when he joined the Pastorian team, especially when it came to the application of rabies vaccines to human cases. Admittedly, Pasteur and Roux somehow managed to put aside, or paper over, their differences when push came to shove. Even

during periods when they were apparently most at odds, their correspondence is stiffly affectionate or at least formally correct in tone. Nor is it always easy to disentangle the scientific vs. clinical split between Pasteur and Roux from other sources of conflict between them. But the task is worth pursuing, not least because it may provide yet another example of the persistent divide between scientific and clinical approaches to the problems of disease, animal experiments, and the ethics of human experimentation.[6]

THE TENSION BETWEEN PASTEUR AND ROUX

No small part of the tension between Pasteur and Roux was "merely" personal. In their physical appearance, political views, and everyday mode of life, they were an odd couple indeed. Pasteur, a sturdily built, financially secure family man with conservative political leanings, was the quintessential "bourgeois"; Roux, a tubercular, ascetic but mercurial "confirmed" bachelor of vaguely leftist or transcendental political views, was the quintessential "bohemian" by contrast. Roux, it might even be said, was a sort of Don Quixote to Pasteur's Napoleon.[7]

Given the personal differences between them, Pasteur and Roux were perhaps bound to clash. Even the personal traits they did have in common pointed toward that outcome: both were stubborn, aloof, severe, demanding of others, quick to take offense, and given to outbursts of temper. And once Roux joined the Pastorian team, their personal differences were exacerbated by a sense of rivalry between master and employee as they worked toward vaccines against anthrax and rabies. Behind the scenes, they were sometimes competing with each other as much as they were collaborating, and there are signs that Roux resented his subordinate role and Pasteur's high-handed treatment of him.

Actually, it is in some ways surprising that Roux ever became part of the Pastorian enterprise in the first place. When he joined Pasteur's laboratory in 1878 at the age of twenty-five, Roux had not yet received the M.D. degree toward which he was struggling despite his straitened financial circumstances. He had been a student of Pasteur's own disciple, Emile Duclaux, at the medical college at Clermont-Ferrand, after which he pursued clinical training in Paris. The French army covered the costs of his medical studies and paid him a modest stipend on the understanding that he would serve as a military physician for ten years after completing his training. In 1877, however, Roux was dismissed from the army for "disciplinary reasons," presumably some form of insubordination.[8]

After his discharge from the army, Roux was making his way, if just barely, by treating poor people for varicose veins, when Duclaux recommended him to Pasteur. Up to that point, Pasteur had selected his research assistants from the pool of postgraduate "agrégés-préparateurs" in the physical sciences at the Ecole Normale Supérieure, in which capacity he had himself served in his youth. Quite deliberately, Pasteur had not yet allowed a medical man to join his team.[9] It is too often forgotten that Pasteur had no M.D. and was not legally qualified to practice medicine. Perhaps partly for that reason, he was openly disdainful of doctors, saying that they were too interested in making money and in high society to meet the rigorous demands of experimental scientific research. Yet now, in 1878, Pasteur decided to expand his tight research circle to include this feisty doctor-in-training who had just been dismissed from the army for insubordination. Why?

The decisive factor, surely, was that Roux had been recommended by Duclaux, Pasteur's favorite disciple and collaborator. But Pasteur had also come to see the need for a veterinarian or medical man as he began to direct the resources of his laboratory toward a frontal assault on the infectious diseases, beginning with anthrax, a lethal and economically significant disease of sheep. A host of experiments on living animals was now in prospect, and Pasteur wanted a research assistant who was at least skilled in the techniques of injection. Thus Roux began his career with Pasteur in 1878 as an animal "inoculator."[10] From the beginning, he performed superbly at his technical tasks, and he was soon participating in the search for attenuated anthrax cultures as well as injecting them into experimental animals.

As we have seen in Chapter Six, visible signs of discord between Pasteur and Roux surfaced during the famous trial of an anthrax vaccine at Pouilly-le-Fort in 1881. The master's conduct in that affair could not have soothed any prior tension between them, and it also gave Roux a clear appreciation of just how boldly, even recklessly, Pasteur was willing to apply vaccines in the face of ambiguous experimental evidence about their safety or efficacy. In this quest for vaccines, as in his earlier research, Pasteur displayed the scientist's attraction to "signals" amid the "noise," and he exuded the bold self-confidence that is often found in scientists who have revealed such patterns to outside acclaim.

Roux, in sharp contrast, proceeded with what I choose to call a clinician's caution in the face of inconvenient or anomalous evidence. In his own research on vaccines, Roux tended to draw carefully limited conclusions from the experimental evidence at hand. When it came to the results of injecting vaccines into living animals, he (unlike Pasteur) expected and even appreci-

ated all the vagaries of their individual responses. As we shall see, Roux was especially circumspect in the case of the application of rabies vaccines to human beings, much to Pasteur's exasperation. As they worked toward a vaccine against rabies, Pasteur and Roux were also headed toward a series of conflicts that once or twice brought them to the verge of complete and permanent rupture. The issues that divided them most deeply had to do with the ethics of human experimentation: specifically, how much evidence of what sort and what degree of reliability should be required from animal experiments before one could justify the application of vaccines to human victims of rabid animal bites?

The most visible sign of an open split between Pasteur and Roux over these issues came at the single most dramatic moment in Pasteur's career: his decision, in early July 1885, to treat Joseph Meister with a vaccine that had thus far been tested only on dogs. For current purposes, the most striking point to notice is Roux's conspicuous absence from the Meister story, which is odd, to say the least. Not only was he Pasteur's leading collaborator on rabies; by then, he had also attained his M.D. degree and was (unlike Pasteur) qualified to practice medicine. He could have treated Meister, had he been asked and willing to do so. In fact, it seems very likely that Roux simply refused to participate in Meister's treatment in any way. And it is equally likely that he did so because he considered Pasteur's treatment of Meister to be a form of unjustified human experimentation.[11] Roux's clinical caution or scruples thus kept him from taking part in what would become the most glorious episode in the Pastorian saga.

Since Pasteur could not himself legally perform the injections on Meister, and since Roux presumably refused to do so, Pasteur had to find more obliging medical men to play that role. As we have seen in Chapter Eight, Pasteur found them in Drs. Vulpian and Grancher. In fact, it was Dr. Grancher, not so incidentally Pasteur's employee, who actually performed the injections on Meister.[12] The participation of Vulpian and Grancher in the treatment of Meister might seem to pose a problem for my suggestion that Roux's clinical background helps to explain his disagreements with Pasteur. After all, Vulpian and Grancher were doctors, too. Like Roux, they had been exposed to the clinical mentality or ethos, and yet they seemed to have few qualms about the proposed treatment of Meister.

But neither Vulpian nor Grancher had Roux's deep experience with rabies. More important, they also lacked Roux's intimate knowledge of the contents of Pasteur's laboratory notebooks. Except for Pasteur himself, no one knew better than Roux just how much and what sort of experimental evidence then existed as to the safety and efficacy of the vaccine used to treat young Meister. In Roux's eyes, quite clearly, the evidence did not justify Pasteur's decision to treat young Joseph Meister with the vaccine in question.

In his famous paper of 26 October 1885, Pasteur tried to meet in advance any ethical concerns about his decision to treat Meister by insisting that he had already made fifty dogs immune to rabies, without a single failure, by the same method he then used to treat Meister beginning on 6 July 1995. Pasteur continued with the following crucial passage: "*My set of 50 dogs, to be sure, had not been bitten before they were made refractory [i.e., immune] to rabies; but that objection had no share in my preoccupations, for I had already, in the course of other experiments, rendered a large number of dogs refractory after they had been bitten.*"[13]

This claim leads us toward a close, if not exhaustively detailed, analysis of Pasteur's laboratory notebooks in order to address three compelling questions about the results of his animal experiments at the time he decided to treat Joseph Meister: (1) Exactly how many dogs had been rendered immune to rabies *after* they had already been bitten by rabid animals? (2) By what method or methods had these dogs been rendered immune and with what rate of success? And (3) exactly what meaning can be attached to Pasteur's claim that he had already rendered fifty dogs immune to rabies "without a single failure" by the same method used on young Joseph Meister? The attentive reader will recall that very similar questions were raised, explicitly or implicitly, by Dr. Michel Peter during the famous 1887 debates at the Académie de médecine.

PASTEUR'S LABORATORY NOTES ON RABIES VACCINES

In Chapter Seven, we were introduced to Pasteur's remarkably empirical, "hit-or-miss" efforts to find a reliable rabies vaccine. Before rabid spinal cords became the focus of his attention, he tested a wide variety of other techniques as well, including the injection into dogs of various quantities of blood and nervous tissue taken from animals dead of rabies. Throughout these early and almost haphazard trials, Pasteur did sometimes produce immune dogs, even when other dogs injected simultaneously by the same method died of rabies. In one fairly typical example from late June 1884—unusual only by virtue of its relatively grand scale—Pasteur injected fourteen dogs subcutaneously with a broth prepared from the brain of a rabbit just dead of a highly virulent rabies virus that had been passed sequentially through fifty-six earlier rabbits. Of the fourteen dogs so inoculated, nine died of rabies but the other five survived and proved resistant to subsequent injections of virulent rabies.[14]

Whenever and however an immune dog emerged from such experiments, Pasteur considered it "vaccinated." By August 1884, he had about twenty-five such dogs, whose immunity he then demonstrated in experiments before the French Rabies Commission, which was appointed that same year at his request. But none of these dogs had sustained rabid animal bites *before* their inoculations, and the methods used on them often resulted in rabies when applied to other dogs. No one outside the Pastorian circle had any way of knowing this fact, including presumably the members of the official French Rabies Commission. By keeping what he called the "details" of his experiments out of public view, Pasteur repeatedly conveyed a misleadingly optimistic impression of the actual results recorded in his laboratory notebooks.

That judgment applies with full force to the results of Pasteur's *post-bite* trials on dogs.[15] Among Dr. Peter's explicit complaints was that Pasteur failed to specify what he meant when he claimed that "a large number of dogs" had been rendered immune to rabies after sustaining rabid animal bites. The first remarkable conclusion to emerge from a close study of Pasteur's laboratory books is that this "large number" was in fact less than twenty. More important, in the course of producing immunity in these bitten dogs—no more than sixteen, by my count—Pasteur failed to save ten dogs treated at the same time and by the same methods. In the case of three or four of the dogs that died despite their treatments, Pasteur believed their deaths resulted from some cause other than rabies and therefore imagined that they could be counted as "successes." This is but one striking example of the wishful thinking, or self-deception, found scattered throughout his laboratory notebooks on rabies. There was obviously no basis for including these dogs among the successfully vaccinated, for they never had a chance to demonstrate their alleged immunity to rabies. At best, a case could be made for excluding them from any list of failures, but only if they were discounted entirely.

More than that, the success rate in these dogs treated after sustaining rabid bites was essentially no different from the survival rate of otherwise similar dogs that were simply left alone after their bites. Actually, in these experimental trials of rabies vaccines, Pasteur hardly lived up to his reputation as a rigorous practitioner of the "controlled experiment." In most cases, he did not employ control dogs at all. While conducting his trials on twenty-six bitten dogs, he used only seven controls. Of these seven dogs left to suffer their fate without treatment, five were still alive at the time Pasteur treated Joseph Meister.[16] One of the surviving five control dogs did eventually die of rabies in September 1885, but by then one of Pasteur's sixteen

Table 9.1 Results of Pasteur's "post-exposure" experimental trials on dogs after they had been bitten by a rabid dog, August 1884 through May 1885

Date	*No. of Dogs Treated after Bitten by Rabid Dog*	*No. of Dogs Succumbing to Rabies*
August 1884	3	0
October 1884	3	2
November 1884	1	1
January 1885	2	1
February 1885	1	0
March 1885	5	2
April 1885	5	3
May 1885	6	1
Total	26	10

"Success" rate: 16/26 = 62%

Controls: Dogs Left Untreated after Bitten

Date	*No. of Untreated Controls*	*No. Succumbing to Rabies*
October 1884	2	0
November 1884	1	1
March 1885	4	2
Total	7	3

"Survival" rate: 4/7 = 57%

allegedly "vaccinated" dogs had also died of the disease after an unusually long incubation period. At any rate, four of the control dogs apparently never did develop rabies. Choosing the most favorable and least favorable interpretations of Pasteur's results, and depending on the precise moment of calculation, it turns out that the survival rates for the two sets of dogs fall into the following ranges: for the dogs treated by Pasteur, 50 to 78 percent; for the untreated control dogs, 57 to 71 percent. (See table 9.1.)

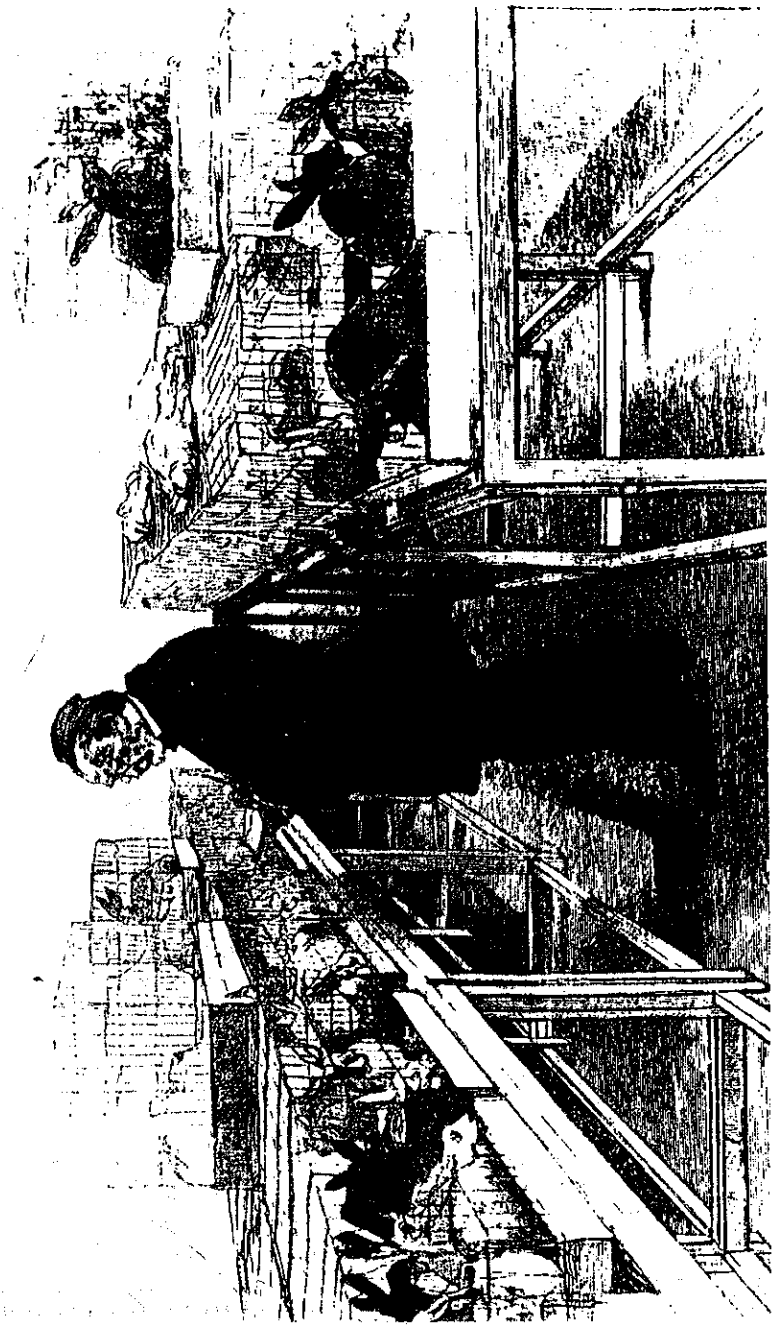
Given the small number of dogs in question (especially in the case of the controls) and the uncertainties of diagnosis and incubation period, the ap-

parent precision of these survival rates is more than a bit specious. But there can be no doubt that the results of these post-bite trials on twenty-six dogs were ambiguous at best. Had Dr. Peter or other critics been aware of these "details," they surely would have asked Pasteur to explain exactly how his post-bite trials provided any justification for the decision to treat Joseph Meister. And the question would have been hard for Pasteur to ignore. For in his famous paper of 26 October 1885 on Meister and Jupille, it deserves repeating here, he openly admitted that of the last fifty dogs he had vaccinated "without a single failure" before treating Meister, *none* had been previously exposed to rabid dog bites. It was, he said, precisely because of the "large number" of other dogs he had already rendered immune after rabid bites that he felt able to put this concern out of his mind.

If this claim already seems odd in view of the actual results of Pasteur's post-bite trials, it becomes more suspect still when close attention is paid to the methods applied to these twenty-six bitten dogs. As we have almost come to expect, Pasteur evaded the issue in public. *When speaking of the dogs he had rendered immune after rabid bites, he said not a word about the method or methods by which this feat had been accomplished.* But the implication, surely, was that they had been treated with injections of desiccated spinal cords. For otherwise, his post-bite trials would seem devoid of any pertinence to Meister's case. Unless the immune dogs had been treated by desiccated cords, why would they have given him any reassurance as he prepared to treat Joseph Meister by that method? True, Pasteur did imply that some sort of distinction could be drawn between the treatment applied to his bitten dogs and the treatment applied to Meister after invariably successful results in the last fifty (unbitten) dogs.[17] But he left the nature of that distinction entirely unclear. In the face of such reticence, it was natural to assume that Pasteur had applied the same method in both cases, but had perfected it in the (unspecified) interval between his post-bite trials and his experiments on the last fifty dogs.

In fact, however, Pasteur had switched to a radically new method in his experiments on this last group of fifty (or perhaps forty) unbitten dogs. It was essentially the technique applied to Joseph Meister beginning on 6 July 1885. But it differed drastically from the methods previously used to treat the twenty-six bitten dogs. As only Pasteur's laboratory notebooks reveal, not a single one of those twenty-six dogs, including of course the sixteen that did develop immunity to rabies, was treated by the method later applied to young Meister.[18] *Actually, the bitten dogs were treated by three different methods, none of which was ever described in print.*

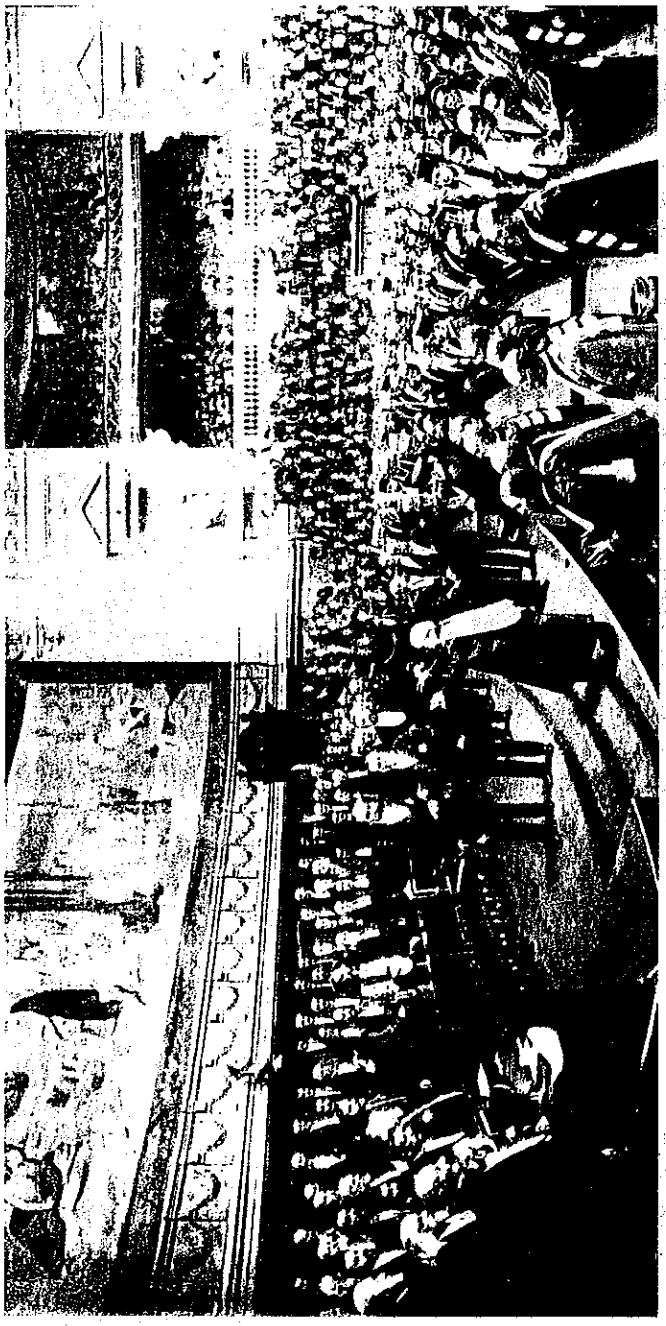
Until 26 October 1885, when Pasteur reported that he had treated Meister and Jupille by injecting them first with dried rabid cords and then with



10. Pasteur observing rabbits injected with the rabies virus. From *La Science illustré*, 15 September 1888. (Musée Pasteur, Paris)

11. Joseph Meister in 1885. (Burndy Library, Dibner Center, Cambridge, Mass.)

12. Jean-Baptiste Jupille in 1885. (Burndy Library, Dibner Center, Cambridge, Mass.)

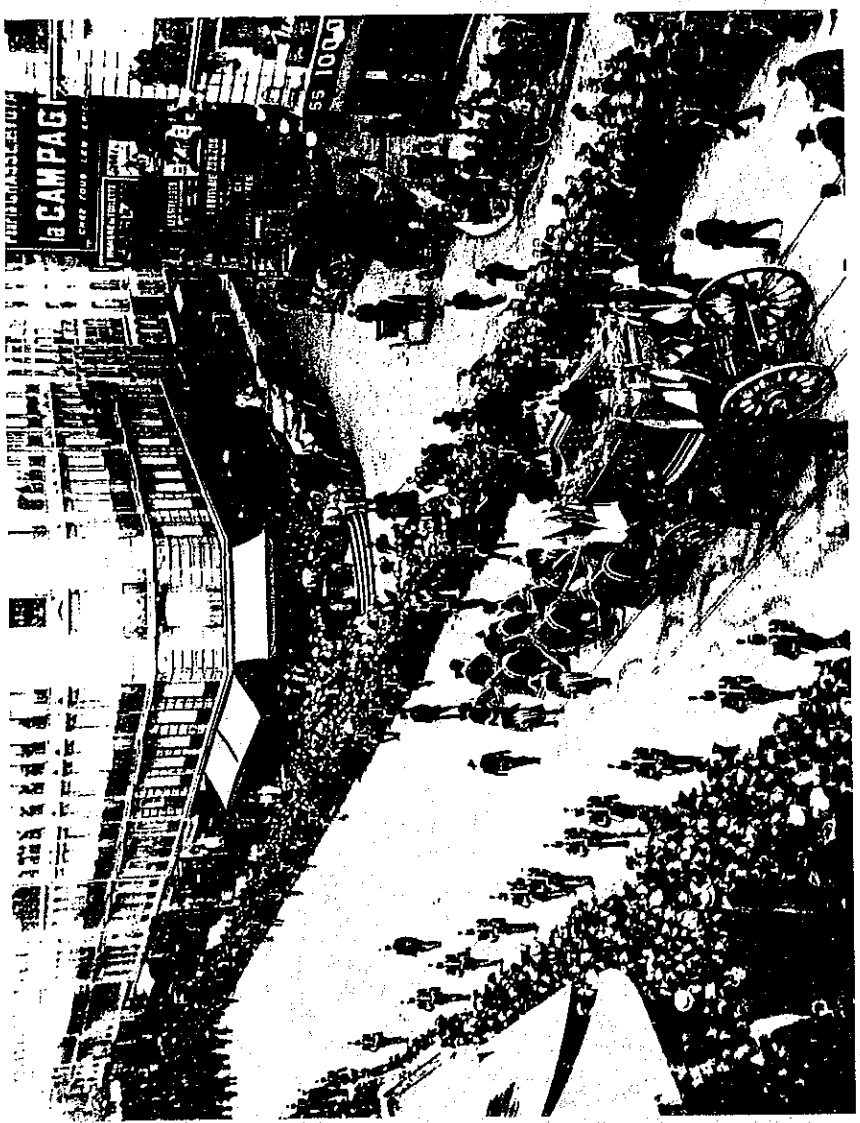


13. From the famous painting by Rixens of Pasteur's jubilee at the Sorbonne. (Musée Pasteur, Paris)

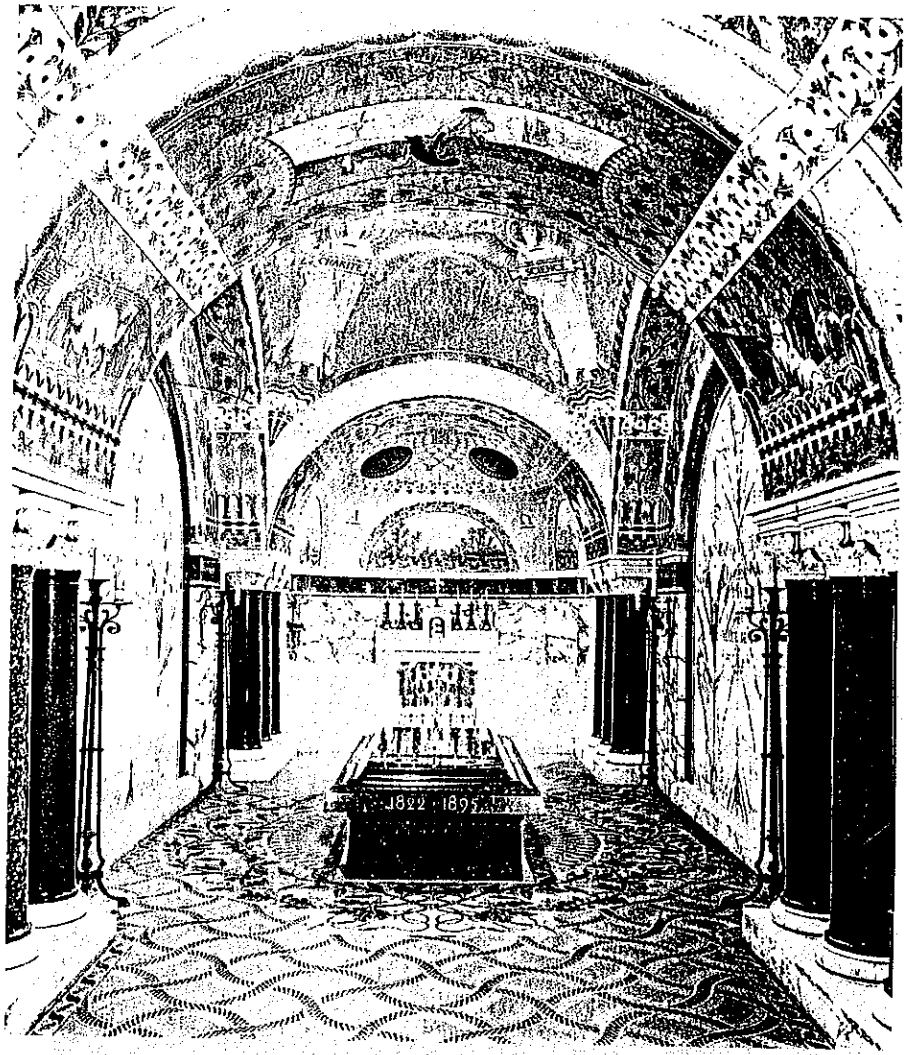
14. Pasteur, in 1892, with his grandson. (Musée Pasteur, Paris)

15. The original building of the Institut Pasteur, inaugurated in November 1888. (Musée Pasteur, Paris)

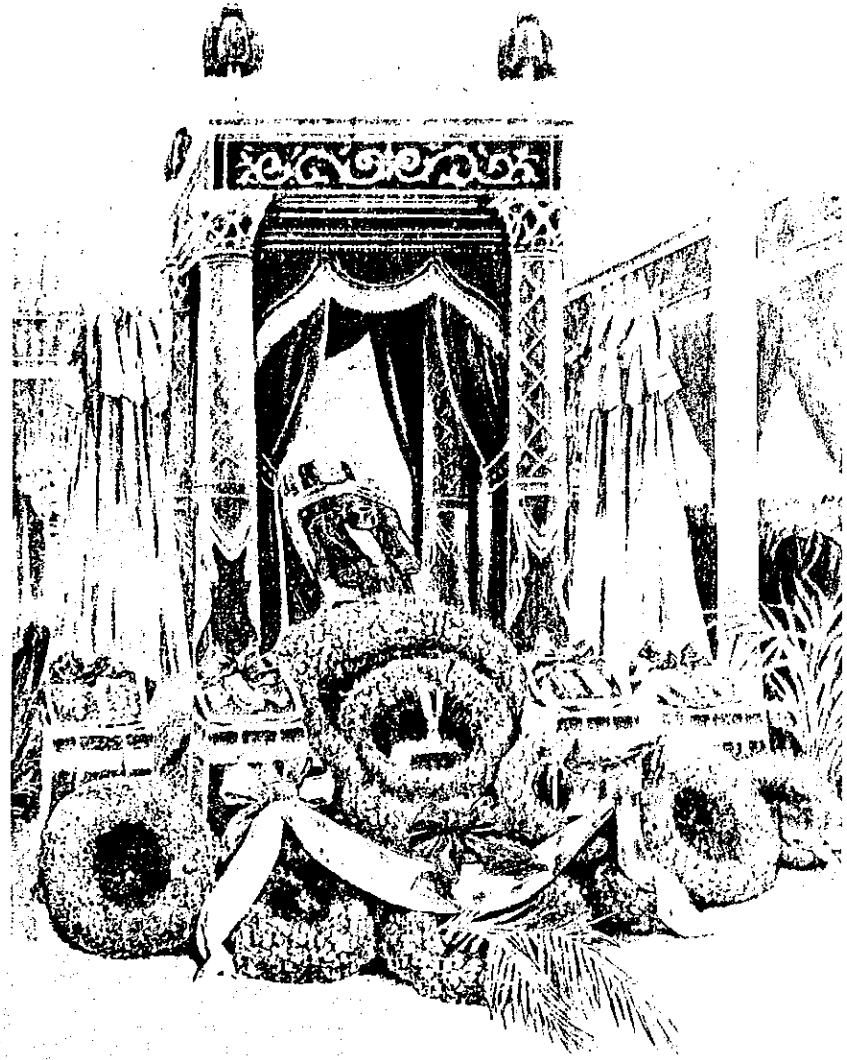
16. Pasteur in 1895, the last photograph taken of him in the gardens of the Institut Pasteur. (Musée Pasteur, Paris)



17. Pasteur's funeral procession through the streets of Paris, 5 October 1895. (Musée Pasteur, Paris)



18. Pasteur's mausoleum at the Institut Pasteur. (Musée Pasteur, Paris)



19. "The Death of Pasteur. Exhibition of the Body at the Institut Pasteur."
(Musée Pasteur, Paris)

20. "La mort du Pasteur," *Le Journal illustré*, 6 October 1895.
(Musée Pasteur, Paris)

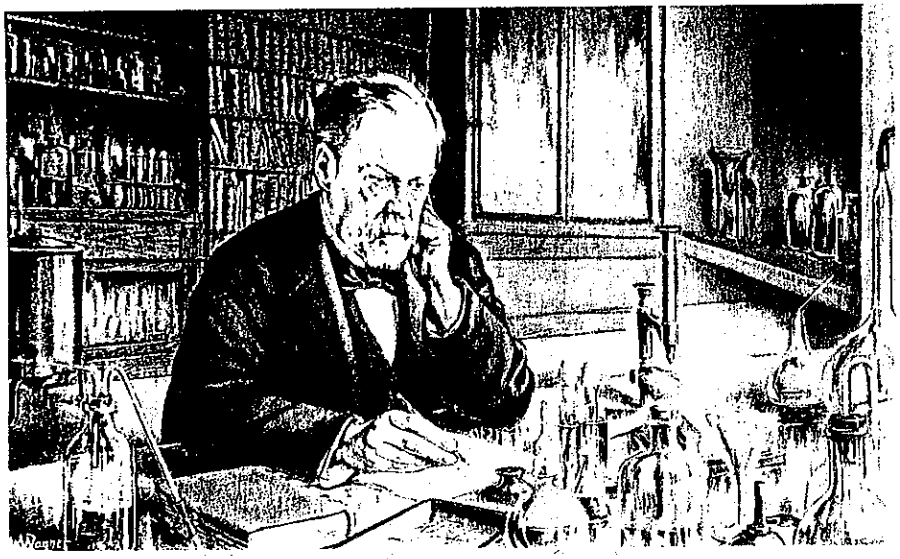
21. "Pasteur est eternal." (Musée Pasteur, Paris)

22. Pasteur as "Benefactor of Humanity." Frontispiece from Fr. Bournard, *Un bienfaiteur de l'humanité: Pasteur, sa vie, son oeuvre.* (Collection of the Library, Wellcome Institute for the History of Medicine, London)

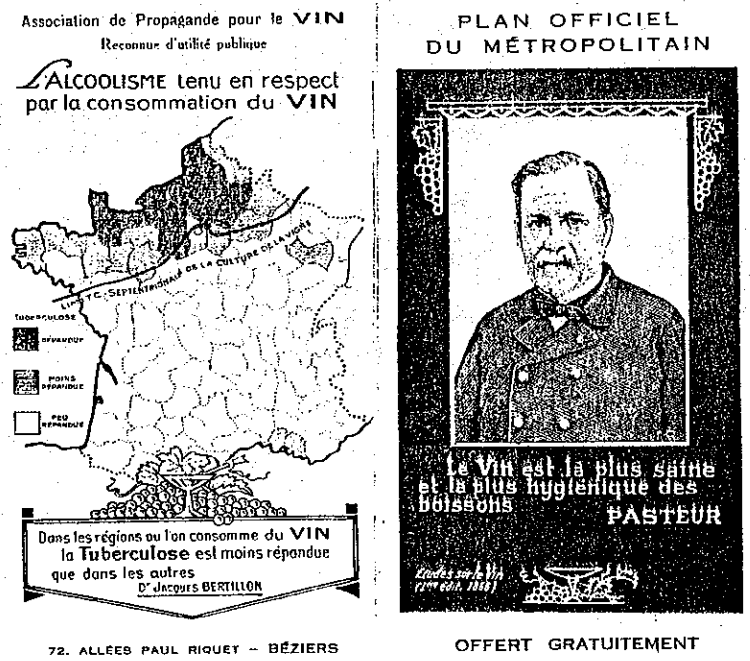
23. "National Homage: From France to Louis Pasteur."

24. "Pasteur Destroys the Theory of Spontaneous Generation." Advertising card for La Chocolaterie d'Aiguebelle. (The William H. Helfand Collection)

25. "Pasteur Discovers the Rabies Vaccine." Advertising card for La Chocolaterie d'Aiguebelle. (The William H. Helfand Collection)



26. Pasteur seated in his laboratory. Advertising card for the Urodonal Company in honor of the centenary of Pasteur's Birth. (The William H. Helfand Collection)



27. "Wine Is the Healthiest and Most Hygienic of Beverages." Advertisement on the official map of the Métro subway system. (The William H. Helfand Collection)

progressively fresher cords, the only announced method was the injection of rabid nervous tissue after it had been attenuated by serial passage through monkeys. When he disclosed this technique in May 1884, Pasteur claimed that the monkey-attenuated vaccine was yielding highly promising results in experiments on dogs.[19] But none of those promising results, it turns out, came from experiments on dogs already exposed to rabid bites. The three methods that Pasteur in fact applied to his bitten dogs are worth revealing here, especially since the third *did* involve the injection of dried spinal cords, but in a manner that differed strikingly from the one used later on Meister. And the special features of this third method will soon lead us into a discussion of Pasteur's theoretical views on immunity, which underwent a dramatic shift as a result of his work on rabies.

PASTEUR AND HIS FIRST METHOD WITH RABID SPINAL CORDS: FROM MOST VIRULENT TO LEAST VIRULENT

Pasteur's post-bite trials, recorded in widely scattered entries in two of his laboratory notebooks, ranged in date of origin from August 1884 to mid-May 1885. His first two methods need not detain us for long. First, in the case of the first seven of the twenty-six treated dogs, the initial inoculation was prepared from the brain of rabbits just dead of a rabies virus that had been augmented in virulence by serial passage through other rabbits. Four of these seven dogs were dead by January 1885, though Pasteur had reason to believe that at least two and perhaps three had died of some cause other than rabies. The three surviving dogs proved immune to subsequent inoculations of virulent rabies.[20] Second, in the next eight treated dogs, the first injection was prepared from the brain of a guinea pig just dead of rabies of more or less ordinary virulence. Of these eight dogs, three soon died of rabies. Once again, the survivors had been rendered immune to rabies.[21]

On 13 April 1885, when the sixteenth bitten dog sustained its first injection, Pasteur began a systematic program of taking spinal cords from rabbits dead of "fixed" or highly virulent rabies and suspending them in desiccated air. From that point through the next five weeks, up until 22 May 1885, when a last group of six dogs received their final injections, Pasteur used these suspended spinal cords as part of a regular series of injections that he hoped would prevent rabies in these last eleven bitten dogs. Seven of the dogs, including five of the last six, were still alive on 16 June 1885. On that day, roughly three weeks after the last six dogs had received their final injections and three weeks before Joseph Meister appeared at his laboratory door, Pasteur "sacrificed" the five survivors so that he could use their cages for

The chart below indicates, in chronological order, some of Pasteur's most significant animal experiments and human trials on potential rabies vaccines using desiccated rabid spinal cords.

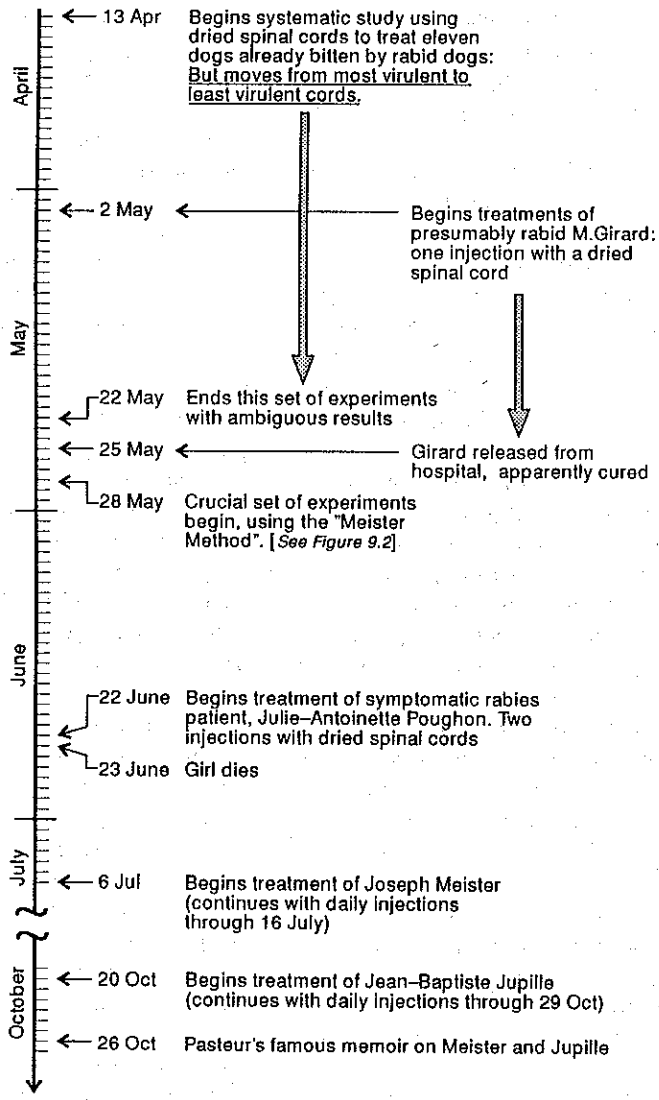


Figure 9.1. Pasteur's path to his rabies vaccine, 13 April 1885 through 6 July 1885: Animal experiments and human trials with dried spinal cords.

other experimental animals.[22] As his experiments multiplied, this practice became increasingly common, the "sacrificed" dogs being dispatched by lethal injections of strychnine. If necessary because space was lacking, this practice nonetheless came at a cost, for these dogs might have developed rabies after an unusually prolonged period of incubation—as some other animals certainly did.

But Pasteur's laboratory notes reveal a much more remarkable and more significant feature of his experimental trials on these last eleven bitten dogs. In all eleven, as noted, injections were prepared from suspended rabid spinal cords. *But here the cords were deployed in a sequence precisely the reverse of the one soon to be adopted in the case of young Joseph Meister.* In Meister's case, Pasteur began with cords that had been drying out for roughly two weeks and then moved to cords that were progressively less dry until, finally, he reached a fresh and highly virulent cord. In the case of the eleven bitten dogs, he began with a fresh cord and then moved to drier and drier cords until, finally, he reached a fully dried-out cord. To anyone familiar with Pasteur's earlier work on other vaccines, this latter modus operandi is astonishing. In developing his vaccines against chicken cholera, anthrax, and swine fever, he had first injected attenuated strains of the implicated microbes and then moved to progressively more virulent strains. Yet here, in these trials with suspended spinal cords on already bitten dogs, he began with fresh, highly virulent cords and only then moved to drier, more attenuated cords. His attempts to prevent rabies in these bitten dogs had now taken a direction precisely the opposite of that followed in all his earlier work on vaccines.

But this *volte-face* is not quite so mysterious as it seems at first sight. For it was associated with a dramatic shift in Pasteur's conception of immunity. In the course of his work on rabies, Pasteur switched from a biological theory of immunity to a modified chemical theory of a sort he had often disparaged when it had been advanced by his critics and competitors. He did so in an attempt to make sense of the variable and sometimes confusing effects that his experimental animals displayed after infection with the rabies virus. The conclusions that Pasteur drew from these confusing effects were themselves more than a bit confusing and susceptible to widely divergent interpretations. But they also bespeak a remarkable flexibility of mind in the now aging Pasteur.

Actually, Pasteur never did invest as much time and energy in efforts to establish a theoretical basis for attenuation and immunity as he did in his more pragmatic, even "empirical," search for effective vaccines. But throughout his work on chicken cholera, anthrax, and swine fever, he linked immunity with the biological, and particularly the nutritional, requirements of the pathogenic organism. In the case of animals inherently

immune to a given disease, he suggested that they presented the invading microbe with an internal "economy," "culture," or "environment" that was inimical to its development, either because their temperature was too high or because they lacked some substance essential to the microbe's life and nutrition. In animals rendered immune by recovery from a prior attack by preventive inoculations (Pasteur's "vaccines"), he supposed that each invasion by a given microbe (even in an attenuated state) removed a portion or all of some essential nutrient, thereby rendering subsequent cultivation of the same microbe difficult or impossible.[23]

But at some point during his work on rabies, Pasteur began to doubt the validity of this biological "exhaustion" theory, at first in the case of rabies and then more generally. According to his own retrospective account, he began to adopt a chemical "toxin" theory for rabies as early as January 1884.[24] A year later, his conversion was largely complete and no longer confined to rabies alone, as is clear from a long and unusually explicit theoretical entry of 29 January 1885 in his laboratory notebook.[25] By then, he was growing increasingly confident that he had made an "immense discovery" of potentially "great generality"—namely, that the living rabies virus produced a dead, soluble, chemical "vaccinal substance" inimical to the further cultivation of the virus and therefore capable of producing immunity to rabies. Thus far, however, Pasteur chose to reveal this new theory only to "those who work alongside me"—that is, Charles Chamberland and Emile Roux, saying that he did not know how to "hide my ideas" from them. Sensibly enough, he planned to expose his theory to others only after it had been thoroughly tested by experiments "already underway."[26]

For present purposes, there is no need to explore the precise extent to which Pasteur's new position was justified by the evidence at hand. Nor is there any need to follow every twist and turn in his experimental and conceptual path to this conclusion. For now, it will suffice to draw attention to the sorts of considerations that lay behind his theoretical conversion and that can help us to understand why he ever tried to treat bitten dogs by moving from virulent (or fresh) to attenuated (or dried) spinal cords instead of the other way around.

The first step in solving the puzzle is to notice Pasteur's increasing focus on the effects of injecting different *quantities* of the same virus into his experimental animals. In trying to make sense of the variable response of individual living organisms to infection with the rabies virus, he began to suspect that the variations depended more on the *amount* of virus injected than on its *intrinsic virulence*. As Pasteur reported in his unusually reflective (i.e., "theoretical") notebook entry of 29 January 1885, he had been led to this belief by two interrelated generalizations that seemed to be emerging

from his experimental evidence: (1) injecting large quantities of a virus of given virulence produced a higher proportion of immune dogs than smaller quantities of the same virus—at least twice as high, by his reckoning; and (2) even when large quantities of a given virus did produce rabies in the inoculated animal, the disease often appeared much later than was usual with smaller quantities of the same virus. This second generalization upset Pasteur's prior assumption that length of incubation depended only on the inherent virulence of the injected virus. Both pieces of evidence thus pointed in the same direction: for a rabies virus of given virulence, the injection of large quantities seemed to produce a higher level of immunity than did the injection of small quantities. Pasteur also suggested that this generalization could explain why rabid dog bites so rarely produced immunity in the bitten dogs, whereas subcutaneous injections of this same "street rabies" into healthy dogs quite often did. The significant difference was that smaller quantities of the rabies virus were transmitted through bites than through subcutaneous injections.

To Pasteur, such results seemed explicable only on the assumption that the rabies virus "manufactured" a nonliving vaccinal substance inimical to its own development. If immunity depended only on the intrinsic and inherited virulence of a living, reproducing rabies virus, then small quantities should produce the same effects as large. Pasteur had not yet managed—nor, indeed, did he ever manage—to separate this hypothetical chemical "vaccinal substance" from the rabies virus that presumably produced it. But as early as January 1885, this was his ultimate hope and goal. At the same time he pondered the possibility that a similar vaccinal substance was produced by the developing anthrax bacillus. In the case of rabies, Pasteur hoped to capture this chemical substance separately from the living virus by filtration. In the case of anthrax, he hoped that the hypothetical chemical vaccine could be found in vitro after the anthrax bacillus had been killed by heating at appropriate temperatures for appropriate periods of time. In both cases, Pasteur had quite suddenly become a convert to the modified chemical theory of immunity that he had so effectively criticized when it was advanced by Auguste Chauveau, Casimir Davaine, and Henri Toussaint, among others. Indeed, the techniques by which Pasteur now sought to isolate a nonliving vaccine against anthrax bear a striking resemblance to the techniques once deployed by his already deceased competitor, Toussaint—though Pasteur declined to say so out loud.[27]

At any rate, Pasteur's inability to separate the hypothetical vaccinal substance from the living rabies virus left him with a delicate task. The goal, of course, was to inject a maximum amount of the alleged vaccinal substance and a minimum amount of living rabies virus. But since no way could be

found to separate the two, the results of any given injection would depend on the relative amounts of living virus and hypothetical vaccinal substance. And since the virus was the presumed source of the vaccinal substance, the quantity of this vaccinal substance perforce depended partly on the amount of virus injected along with it. If the amount of injected virus was too small—as in the case of rabid dog bites—so too would the quantity of vaccinal substance be too small to produce immunity. In such a case, the supply of vaccinal substance would be inadequate to prevent the further development of the virus, and rabies would thus eventually appear in the inoculated animal.

Although Pasteur was understandably reluctant to say so himself, this interpretation of his results had the advantage for him of being almost infinitely flexible. Almost any result could be explained by adopting appropriate—and unverifiable—assumptions about the relative amounts of living virus and associated vaccinal substance. By the time Pasteur presented his modified chemical theory of rabies immunity in print—briefly in the famous memoir of 26 October 1885 on Meister and Jupille, and more extensively in a paper of January 1887[28]—he had adopted the technique of beginning with dry rabid spinal cords and moving to progressively fresher ones. As Pasteur pointed out, most commentators assumed that this technique was equivalent to beginning with a highly attenuated virus and only then moving to more virulent strains. But he argued instead that the vaccinal properties of his cords depended not on the inherent virulence of the virus they contained—indeed, the virulence might be the same in all of the cords, dry or fresh—but rather on the relative amounts of living virus and vaccinal substance in them. Specifically, Pasteur suggested that the drying process might somehow reduce the *amount* of living virus—without changing its virulence—more rapidly than it reduced the amount of nonliving vaccinal substance. And so, after a period of roughly two weeks, there might remain enough vaccinal substance to prevent the reduced amount of living rabies virus from developing further and thus giving rise to rabies. Ideally, of course, one would prefer to use spinal strips in which all of the living virus had been destroyed while some vaccinal substance still remained. And Pasteur predicted that such a "dead" vaccine against rabies would one day be found, though he had not yet been able to perfect one himself.

But in January 1885, when Pasteur also expressed the hope that he might someday isolate a "dead" rabies vaccine, his interpretation of rabies immunity was very different from the one he had settled on two years later. So, too, were the techniques by which he then sought to produce immunity in his experimental animals. His laboratory notes from early 1885 make it

abundantly clear that a reliable rabies vaccine continued to elude him. Well into the spring of 1885, he had still not settled on any one approach to the problem. He continued to inject dogs, bitten and unbitten, with several very different sorts of potential vaccines—and the results were inconclusive and confusing.[29] True, Pasteur had for some time displayed a special and growing interest in the possibilities of a vaccine prepared from desiccated spinal cords. In his notebook entry of 29 January 1885, Pasteur even referred to experiments with desiccated spinal cords of low virulence as perhaps the most important test for his new chemical theory of rabies immunity. But he had not yet begun systematic trials of such potential vaccines. And if his laboratory notebook thereafter devotes increasing attention to desiccated spinal cords, it also reveals that he long remained uncertain about the precise point at which desiccated cords might become at once nonlethal and capable of producing immunity when injected into dogs.

In fact, the experiments actually recorded in Pasteur's laboratory notebook through mid-May 1885, including especially his trials on bitten dogs, suggest that even then he remained uncertain about the basic issues raised in his notebook entry of 29 January 1885. From that point on, he made several more or less systematic attempts to compare the effects of injecting large and small quantities of rabid nervous tissue of presumably constant virulence—the very issue that had pointed him toward his new chemical theory of rabies immunity in the first place. Another related issue—more salient for the moment—concerned the speed with which immunity had to be achieved if there was to be any chance of success in the life-and-death struggle against the rabies virus.

In his notebook entry of 29 January 1885, Pasteur endorsed the position that immunity had to be established quickly—perhaps as soon as the eighth day, certainly no later than the fifteenth—if a dog was to escape the lethal effects of exposure to the rabies virus.[30] To judge from the experiments recorded in his laboratory notes from that point through mid-May 1885, Pasteur seemed then to assume that virulent strains of the rabies virus—or, more precisely, fresh rabid spinal cords—might produce immunity more quickly than drier cords. At this point, unlike two years later, Pasteur presumably thought that fresh rabid spinal cords might contain a greater quantity of his hypothetical vaccinal substance than drier cords. In any case, he often chose to begin his series of preventive inoculations with a very fresh cord (what he would, at other times, call "a highly virulent" virus), presumably in the hope that it would produce immunity quickly. A striking example of this practice is found in his last eleven post-bite trials on dogs. In all of them he began the series of injections with a highly virulent (fresh) rabid

spinal cord and only then moved to less and less virulent (i.e., or drier and drier) cords.[31]

Within a few months, however—certainly by April 1885—Pasteur began to notice that the incubation period of rabies in at least some of his experimental animals was more prolonged when they were injected with dry instead of fresh cords, which presumably meant that dry cords conferred some degree of immunity in the case of some animals.[32] For quite some time, Roux had noticed the same trend, although a range of experimental contingencies, including especially the ambient temperature, could easily obscure any clear pattern.[33]

But could Pasteur have had this vaguely emerging pattern in mind when, on 2 May 1885, he decided to treat M. Girard, his first rabid "private patient"? The evidence is circumstantial, to be sure, and Pasteur's laboratory notebooks do not explicitly indicate that the results of such animal experiments lay behind his decision to treat Girard with a highly desiccated spinal cord. What we do know for sure is that within three days of Girard's release from the hospital—presumably "cured" of rabies by just one such injection—Pasteur suddenly undertook a systematic series of experiments in which dogs were "treated" by a sequence of injections that began with very dry spinal cords and ended with very fresh cords.

If Girard's presumed "cure" did inspire or encourage this new experimental program (to repeat a suggestion made in Chapter Seven), it would seem that Pasteur was once again exceptionally lucky, especially given that the diagnosis of rabies in M. Girard was almost surely mistaken. But I suspect that Pasteur, were he here to defend his work, would insist yet again not only that chance favors the prepared mind, but also that "luck comes to the bold."[34]

PASTEUR'S EXPERIMENTS ON DOGS BY THE "MEISTER METHOD": LEAST VIRULENT TO MOST VIRULENT SPINAL CORDS

In any case, Pasteur's laboratory notebooks amply confirm that, at the time he undertook to treat Meister, he had not yet produced anything remotely approaching "multiple proofs" of the efficacy of his method on "diverse animal species." But that is the least of it. For the notebooks also reveal that Pasteur had not yet met the much less demanding criteria to which he referred in his famous paper on the Meister case, three months after the boy's treatment had been completed.

In fact, the notebooks provide no evidence that Pasteur had actually completed the animal experiments to which he appealed in justification of his

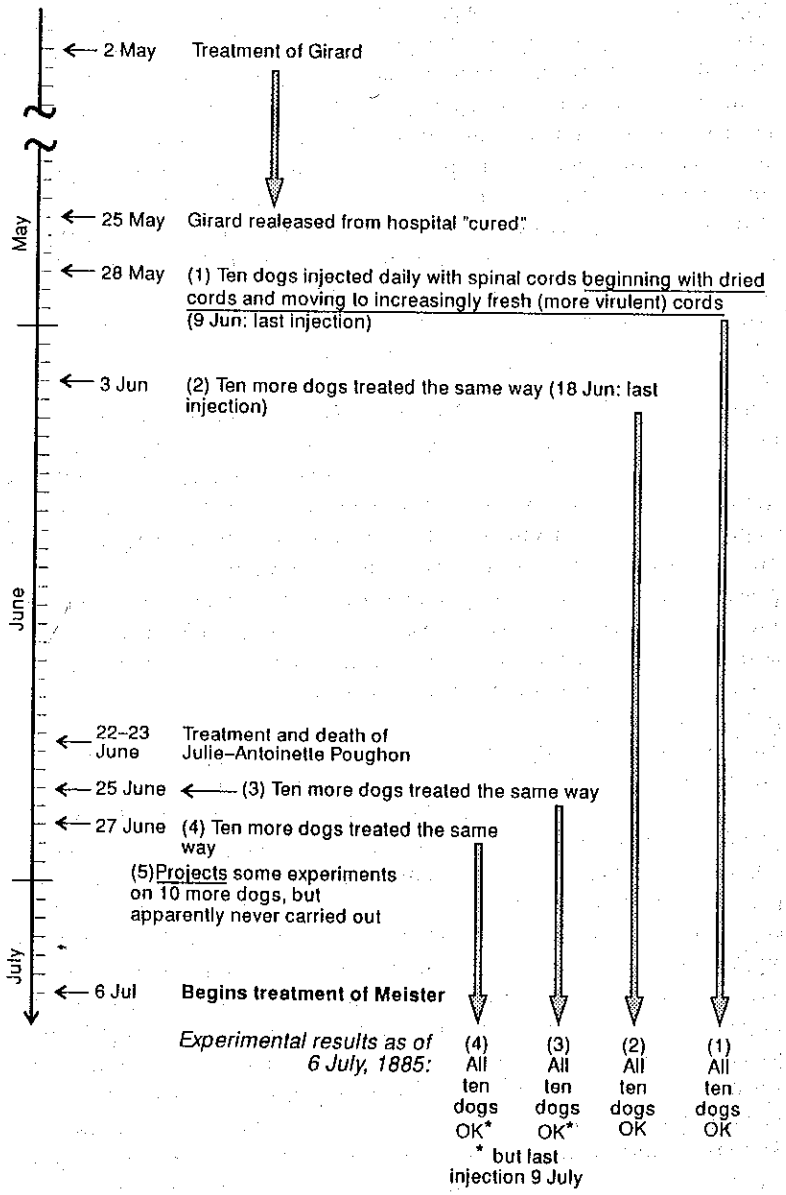


Figure 9.2. The results of Pasteur's experiments on dogs treated by the "Meister Method," 28 May 1885 through 6 July 1885.

decision to treat Meister. Rather, they show that as of 6 July 1885, when Meister's treatment began, Pasteur had just *begun* a series of vaguely comparable experiments on forty dogs (and conceivably on fifty, though I have not yet been able to identify these last ten dogs). As of that date, according to the laboratory notebooks, only twenty of the forty to fifty experimental dogs had even completed the full series of "vaccinal" injections. And none of the dogs had survived as long as thirty days since their last (and highly lethal) injection. (See fig. 9.2.) From a few earlier experiments, Pasteur might reasonably have surmised that rabies symptoms typically appeared between the seventeenth and twenty-sixth day in dogs inoculated with highly virulent rabies virus. That these twenty dogs had not yet displayed fatal symptoms of rabies, three to four weeks (twenty-three to thirty days) after they had been injected with a highly virulent rabies virus, was the best evidence Pasteur had of the safety and efficacy of his antirabies vaccine at the time he decided to treat young Joseph Meister.[35] Furthermore, as Pasteur himself conceded, not a single one of these experimental dogs had first been bitten or otherwise inoculated with rabies before being "treated" by the method used on Meister.

Against this background, it should come as no great surprise that Pasteur never did publicly disclose the state of his animal experiments on the "Meister method" as they stood at the point at which he decided to treat the boy. Nor, indeed, have they been revealed in print until now. They are recorded only in Pasteur's private notebook of that period, which, like the other one hundred laboratory notebooks he left behind at his death in 1895, remained in the hands or control of his immediate family until the mid-1970s. Even now, the notebooks have only begun to be subjected to the close scrutiny and analysis they deserve.

But it is already clear, and should not surprise us, that the most acute critics of Pasteur's treatment for rabies were medical men. Even Dr. Grancher, who performed the injections on Meister and other early subjects of the Pastorian treatment, later admitted that "the great majority of doctors did not believe in [Pasteur's] antirabies vaccine."[36] If some of these critical doctors were motivated in part by personal hostility toward Pasteur and by their concern over the intrusion of the new experimental science into their traditional domain, they also directed sometimes telling attention to the pertinent ethical issues, and their cautious skepticism clearly owed something to the clinical ethos or mentality they shared with Roux. In fact, as Dr. Peter suspected and as Dr. Roux knew full well, the decision to treat Meister was ethically dubious by then prevailing standards, as was some of the rest of Pasteur's conduct in his headlong and headstrong quest for vaccines.

ROUX AND PASTEUR AFTER MEISTER: PARADOXES AND PUZZLES

The story just told leaves one or two puzzles unresolved. For if Roux had such deep and long-standing misgivings about Pasteur's conduct, including notably the decision to treat young Joseph Meister, why did he return to the master's laboratory a few months later to participate in its subsequent work on rabies? And why did he keep his misgivings private, even after Pasteur's death? Despite Roux's alleged concern with ethical issues, did he not himself take part in a lifelong "cover-up" of the real Pasteur and the real story of his work on vaccines?

Let us begin with the first of these questions, which is perhaps the easiest to answer. Why *did* Roux return to Pasteur's laboratory and its work on rabies? To ethical absolutists or conspiratorial muckrakers, the answer may come as something of a disappointment. For Roux's return is probably best explained by the simple fact that he came to believe in the overall safety and efficacy of the original Pastorian vaccine. To be sure, Roux continued to have serious differences with Pasteur over matters of detail and about particular cases. Even when he did rejoin the Pastorian rabies team, he retained much of his clinical skepticism. On balance, however, he had become a convert to Pasteur's cause.

One powerful factor, of course, was the increasingly evident success of Pasteur's vaccine in almost all human cases. But Roux may have been even more impressed by the rapidly expanding body of favorable evidence from animal experiments. For Pasteur had by no means abandoned or curtailed his animal research on rabies in the wake of his celebrated success with Meister. And the evidence from those later animal experiments seemed to vindicate Pasteur's original intuition. Once again, or so Roux had now come to believe, Pasteur had been "on the right track" even before his experimental evidence was fully convincing to others. Luckily for Pasteur, Roux's "conversion" came just in time to offset a swelling tide of criticism from Dr. Peter and other clinicians.

In a very revealing letter of 4 January 1887, on the eve of the debates with Dr. Peter at the Académie de Médicine, Roux advised Pasteur that he could spare himself much "trouble and fatigue simply by extracting from your notebooks the details of the experiments on the vaccination of dogs already bitten [i.e., healthy dogs that survived rabies after having been inoculated with the virus through the bites of rabid dogs]." Those experiments, Roux continued, "are capital and justify the application of the method to man."[37] Inexplicably, Pasteur never did follow this sage piece of advice.

In any case, Roux's letter suggests that by January 1887 he had become convinced that the accumulated evidence from animal experiments was now sufficient to establish the basic safety and efficacy of Pasteur's treatment for rabies. By then, somewhat paradoxically, Pasteur had already benefited from Roux's prior skepticism about the treatment, which was well known to those within and close to the Pastorian circle. The most spectacular example of this paradoxical benefit came in the case of one of Pasteur's most blatant "failures," a boy who had died of rabies in October 1886 in spite of, or even because of, the Pastorian treatment. Here again Pasteur's conduct seems ethically dubious, and here again the episode remained private until disclosed a half century later by his nephew Adrien Loir.

According to Loir, whose basic credibility we now have good reasons to accept, Roux discovered, through animal experiments carried out with material taken from the boy's brain upon autopsy, that the boy had died of rabies. Without knowing of this evidence, the boy's aggrieved and angry father had already accused Pasteur and his collaborators of killing his son and threatened to sue. Loir reported that Pasteur, then resting at a villa in Italy for the sake of his fading health, listened calmly to the circumstances of this case, with "serene" confidence in his method of treatment. Given his usual caution and clinical mentality, Roux was almost surely less serene, but he nonetheless placed himself on Pasteur's side at this crucial juncture. With the collusion of other authorities, Pasteur and Roux managed to keep the full circumstances of the boy's death out of the public eye, and no legal action was taken. Toward this end, Roux's participation was crucial.[38]

Even so, Roux continued to display his clinical caution. He and Pasteur still disagreed, especially because Pasteur had introduced a modified version of his original treatment in cases where subjects had been severely bitten (especially by wolves) or had presented themselves for treatment only after a long delay. Roux was clearly skeptical about this new "intensive method" of treatment, as Pasteur called it. It seems likely that Roux's skepticism was based partly on his usual concern for convincing evidence from prior animal experiments. He was especially concerned about Pasteur's cavalier resort to highly virulent cords in such cases. In a letter of 10 April 1887 to Dr. Grancher, having perhaps heard once too often of Roux's reservations about the "intensive method," Pasteur wrote that "Roux is decidedly too timid." "I understand his scruples," Pasteur continued, "without accepting them [*sans les approuver*]."[39] For me, no single piece of documentary evidence better captures the difference between Pasteur's scientific as opposed to Roux's clinical mentality. It is powerfully reinforced by the testimony of Dr. Grancher, who several years after treating Joseph Meister had this to say about Pasteur's approach to rabies vaccines: "*Pasteur lacked prudence in medical matters. He had made no reservations as to the possibility of partial failures [of his rabies vaccine]. Had he been a doctor, he would have instinctively taken some precautions by foreseeing the possibility of [occasional] failures.*"[40]

ROUX'S PUBLIC RETICENCE ABOUT PASTEUR'S CONDUCT: ANOTHER SIGN OF HIS CLINICAL MENTALITY?

This brings us, finally, to the other puzzles posed at the outset of the preceding section. Those questions can be collapsed into one: Why did Roux remain forever in the Pastorian fold and forever silent about Pasteur's ethical indiscretions, some of which came at his own expense? This question, which has no easy answer, gains in force when we recall that Roux did not merely choose to conceal what he knew about the less savory features of Pasteur's conduct in the quest for vaccines. Quite the opposite. Roux played an active part in the construction of the heroic legend of Louis Pasteur. Whatever he may have said to his own disciples in private conversation, Roux was a staunch public defender of the Pastorian faith.

Surely part of the explanation lies in the fact that Roux's own career and reputation were so closely linked with Pasteur's. While it seems unlikely that the bohemian Roux was concerned about "job security" in any usual sense, he clearly did become increasingly protective of the reputation of the enterprise with which he had been associated throughout his career and which was, after all, the main source of his claim to fame.

In the end, however, I would like to suggest that another part of Roux's protective public stance toward Pasteur can be ascribed to the very clinical sensibility that brought him into conflict with the master in the first place. To the extent that Roux retained vestiges of that mentality, he would have been sensitive to the sometimes irrational forces that drove the ill and aging Pasteur. To the same extent, he would have been reluctant to disclose the master's ethical indiscretions after Pasteur's death. Most important, perhaps, Roux's "clinical" tolerance for ambiguity may have allowed him to appreciate the virtues of the Pastorian enterprise as a whole even if he sometimes objected to the means by which its founder had achieved his ends. Perhaps he appreciated, more than Pasteur himself, the exquisite ethical dilemmas the master had faced.

For the sake of history and his own place in it, Roux's clinical mentality, if that's the right word for it, came at a cost. Like his students Charles Nicolle and Emile Lagrange, historians may wish that Roux had been less "scrupulous," or more forthcoming, about his long-standing disagreements

with Pasteur. Had he chosen to do so, Roux could easily have produced a revealing, even scandalous, public exposé of Pasteur's conduct. By choosing to do otherwise, indeed the opposite, Roux may well have confirmed Pasteur's judgment that he was "decidedly too timid." But we can appreciate, in a way that Pasteur could not, just how much the Pastorian enterprise would benefit from Roux's clinical sensibilities. And we would not expect Roux to display that mentality vis-à-vis Meister only to abandon it in the case of Pasteur himself.

PART IV

The Pastorian Myth