THE EIGHTEENTH CENTURY, which was to conclude with the American and French Revolutions, was also the Age of Enlightenment. The conviction was growing that scientific progress was intended to enable humans to control the world around us: Had we not learned to control thunderbolts, thanks to the lightning rod? This was the era of Linnaeus, Buffon, and Diderot, and we began cataloguing nature's riches and seeking to employ them in a more rational way.

This approach was seen particularly in the areas of agriculture and animal husbandry. Improved productivity was the order of the day. Landowners organized and agricultural societies and academies were founded, where questions of farming were discussed and where news and information were exchanged and documents published. In England, the enclosure policy was broadly implemented, evicting small-scale farmers to the benefit of big landowners and providing the latter with the resources for long-term investment. In the sphere of animal husbandry, major efforts were made to improve feed and conditions, and to select the most productive breeds.

Sheep farming was the first beneficiary of this modernization because wool production was a major industry not only in England but
throughout Europe. It is estimated that a quarter of the English population was involved in wool production or the wool trade in one way or another. And that sector was to remain important. Toward the end of the nineteenth century, an eminent French veterinarian, while noting that sheep farming was on the rise for purposes of meat production, wrote this:

Wool is among the pillars of the well-being of modern-day societies. We may thus venture to say that the people who produce the most wool will be the richest and perhaps the most powerful. For more than fifty years, wool production has rained showers of gold upon Europe: For Germany and Russia, it has provided hitherto unknown material well-being and the hope of future prosperity. As for England, is it not its countless merinos that must be deemed accountable for the wealth of its colonies and the magnificence of its trade beyond compare?¹

Given the care lavished upon these wool-bearing creatures, is it any surprise that the diseases that could affect them were also the object of attention? They had to be catalogued in the hope of being able to conquer them. Thus, the existence of The Disease was first reported in the 1730s, as we can see from the following, written in 1772 by the Reverend Thomas Comber, on the subject of an ovine disease that he referred to as rickets:

The principal Symptom of the first Stage of this Distemper, is a Kind of Light-Headedness, which makes the affected Sheep appear much wilder than usual, when his Master or Shepherd, as well as a Stranger, approaches him. He bounces up suddenly from his Laire, and runs to a Distance, as though he were pursued by Dogs, &c. . . .

In the second Stage of the Distemper, the principal Symptom of the Sheep is his rubbing himself against Trees, Posts, &c. with such Fury as to pull off his Wool and tear away his Flesh.

The distressed Animal has now a violent Itching in his Skin . . . but it does not appear that there is ever any cutaneous Eruption. . . .
The third and last Stage of this dreadful Malady seems to be only the Progress of Dissolution, after an unfavourable Crisis. The poor Animal, as condemned by Nature, appears stupid, separates from the Flock, walks irregularly, (whence probably the Name of this Disease, Rickets) generally lies, and eats little. These Symptoms increase in Degree till Death, which follows a general Consumption.

I do not find, Sir, that this Distemper is infectious: but alas! it is hereditary, and equally from Sire and Dam; and, like other hereditary Distempers, may lie latent one Generation and then revives with all its former Fury.

It is an incontrovertible Point, that whatever Sheep is once seized by this Distemper, never recovers; and it seems almost as incontrovertible, that whatever Sheep escapes it in his first Years, never takes it.

This Distemper is generally said to be of about forty Years standing in England; and the Shepherds of this County pretend to trace it from the neighbouring County of Lincoln hither.

And forty years before 1772 would take us to 1732. Independent confirmation of the presence of The Disease in Lincolnshire in the first half of the eighteenth century is found in a 1755 report addressed to the House of Commons by sheep farmers of that county. The report states that a disease here too called rickets—or shaking—had been affecting their flocks for ten years; that the disease was transmitted by rams; that it was often “in the blood” of their animals a year or two before it was detectable; and that once it had manifested itself, it could never be cured. The farmers wanted measures to be taken against jobbers (speculators who had gained a monopoly on the trade in sheep) who mingled sick with healthy animals.

Following those early descriptions, the existence of The Disease was repeatedly reported through the late nineteenth century in Great Britain, Germany, and France. Oddly, it seems every so often to have
been rediscovered as a new disease, which caused it to acquire numerous names. By the end of the nineteenth century, the English had settled on the name *scrapie*, and the French on *tremblante* ("the shakes").

The fact that the disease was seemingly forgotten between rediscoveries was due in large part, it appears, to its having been considered so shameful that farmers took great pains to conceal it. A single animal suffering from The Disease cast suspicion on the entire flock, considerably diminishing its value. For the farmer, it was both an economic disaster and a blemish on his honor. It must be said that the sight of a stricken animal was a poignant one, especially in the final stages of the disease. Here is a description written in 1937 by three prominent French veterinarians—Ivan Bertrand, Henri Carré, and Felix Charles Eugene Lucam—which is more detailed than Comber's account of a century and a half earlier but is clearly describing the same disease:

When an animal is stricken, it scratches frantically, vigorously rubbing its tail, rump, lower back, and back against the walls or against its trough. Sometimes, it sits like a dog and energetically rubs the hind portions of its legs against the ground. Using its hind limbs, it scratches its head and the forward parts of its body. Using its teeth, it scratches the lower parts of its limbs. A continual victim of this generalized and persistent itching, the animal spends all its time trying to scratch itself, no matter how....

If the skin is examined at this stage of the disease, absolutely no lesions will be found: its smoothness, fineness, and coloring are intact, and it is absolutely impossible to connect this itching to a cutaneous cause.

The sick [animals] seem bewildered and have a wild look in their eyes. Some suddenly begin to run, as if frightened, without cause. When they are alone and can be observed without their suspecting the presence of an observer, for example in the sheepfold, they are seen to be sometimes immobile, head high, ears alert, gaze fixed, as though they were hearing a distant noise. Then they suddenly jump and wildly make to flee an imaginary threat. During such flight, the
gait is most particular: the head is held very high, and the forelegs are flung far forward in order to cover ground.

Their bleating is altered: indistinct, tremulous, and weak. In most cases, even the lightest touch, especially on the hindquarters, or the approach of a person or a dog will cause shuddering, quivering, or even intense and prolonged shaking. It is this localized or generalized muscular shaking that gives its name to the disease: tremblante.

A second stage [of the disease] is characterized by more pronounced shaking of the head and the muscular system, by general weakening, by the appearance of secondary lesions from scratching, and above all by a new symptom: lack of coordination in movement. Appetite, which has been steady until this point, begins to decrease; the animal loses weight and muscle tone decreases; this is the beginning of the cachexia [emaciation] that will continue to increase and that will become extreme in the final stage. Because pruritis [itching] becomes more intense, the animal rubs, scratches, and bites itself to the point of damaging the skin. Owing to the constant rubbing, the wool becomes brittle and wispy and eventually is torn out over large areas. In those bare areas, the irritated skin reddens, thickens, wrinkles, and is covered with scabs. Scratches and open wounds appear, and there suppuration begins.

The animal is soon in an appalling state of emaciation and uncleanness, with remnants of shaggy fleece and bare skin covered with scabs.

Then lack of coordination in movement is seen: gradually the sick [animal's] gait becomes unsure and hesitant; it remains in the rear of the flock and follows it with difficulty; it stumbles with every step. Locomotive disorders are to be observed especially in the hind legs, which move with difficulty and are stiff. If its gait is quickened, movement is confused, with the forelegs trotting and the hind legs galloping. Falls are frequent.

In the third stage, all the symptoms previously mentioned grow worse. [The animal] staggers as though drunk, and prefers to remain lying in a corner. Sometimes, when it is forced to stand unaided, it will remain immobile, its limbs spread, its head lowered,
and its body gently swaying as though it were trying to keep its balance on a moving platform; then, zigzagging with difficulty, it will reach a corner where it will fall in a heap, often uttering a moan.

In the final stage, rising and moving about become impossible, and the sick [animal] is able only to crawl on its knees. Emaciation is extreme and appetite has completely disappeared. Often, fetid and exhausting diarrhea sets in. The animal ends by stretching full out on its side; occasionally, it moves its limbs—which indicates clearly that paralysis never occurs. . . . Body temperature decreases, and death occurs without death throes, with complete physical decline.

We note that no thermal reaction is present at any point in the disease. . . .

The time between the appearance of the first symptoms and death can be from six weeks to six months. On average, it is about three months.4

That description echoes the symptoms set out by many writers since the early eighteenth century. The relative importance attributed to the various symptoms is, however, not constant, and this is reflected in the variety of names for the disease. Scrapie comes from “to scrape,” laying stress on the apparently unbearable itching to which affected animals are prey, which causes them to scratch wildly to the point of tearing out patches of wool. That is the symptom highlighted also in the old French term prurigo lombaire, lumbar prurigo (“prurigo” being any of several kinds of itchy skin eruptions). On the other hand, other names used in France—such as maladie convulsive, maladie folle (mad), maladie nerveuse, maladie chancelante (wobbling), névralgie lombaire (lumbar neuralgia), trembleuse, and, of course, the current term tremblante—focus on neurological symptoms: The nervous system is obviously affected. That aspect of the disease is reflected also in another, rather euphonious, term used in France, vertige du mouton—ovine vertigo or “sheep dizziness”—as well as in the most common German term, Traberkrankheit. Traber means “trot,” and the name reflects the characteristic gait of sick animals.
Because of this diversity in the way the symptoms were perceived, only very belatedly was it realized that this was but one disease. It also makes it risky to identify scrapie among the ovine ailments described before the eighteenth century and even casts doubt on the true nature of diseases described as scrapie or *tremblante* in the eighteenth and nineteenth centuries. Indeed, some symptoms of scrapie, taken in isolation, could be confused with those of other diseases.

Such uncertainty is one reason why it is so hard to date scrapie’s arrival in western Europe. Some suggest that it came with the importation of merino sheep from Spain with a view to producing high-quality wool. This took place in England early in the eighteenth century, but in France not until the end of that century, which would seem to correspond to the dates of the first descriptions of the disease in each country. Others question the involvement of these merinos, and consider that their importation merely occurred when great attention was beginning to be paid to sheep farming, which in turn led to detection of the disease. In any event, most people agree that scrapie would have existed in Germany and central Europe before merino sheep were introduced to those areas.

For the farmers and veterinarians of the day, the key problem was to find a response to the disease, which could claim between 5 and 10 percent of some flocks. The disease was always fatal, and no matter what treatment was tried, it failed. It was important first and foremost to understand the cause of the disease so as to be able to protect animals from it. Here, there was disagreement, to say the least. Some saw scrapie as an infectious disease, some thought it was hereditary, and others linked it to environmental factors, diet, or the conditions in which the animals were bred.

Among the proponents of the infectious nature of the disease was a German writer who, in 1759, suggested that the best solution for a sheep farmer who discovered one of his animals to be suffering from scrapie was to remove it immediately from the flock, slaughter it—and use the meat to feed the servants. He added that the sick animal
should be isolated without delay because the disease was contagious and could cause grave damage in the remainder of the flock.

Others entirely rejected the notion of contagion—noting, for example, that in a given flock the offspring of some rams were affected while those of other rams were not. From this they concluded that the disease was hereditary.

Then there were those who believed in neither contagion nor heredity, including one Monsieur Lezius, whose opinion was described in 1827:

From his very precise observations, Monsieur Lezius concluded that vertigo in ewes results from an evil practice followed at the time of mating, and that this disease particularly affects ewes sired by excessively ardent rams which, in their overexcited state, are prevented from adequately satisfying their reproductive instincts. Such rams, enabled to cover only one or two ewes a day, will have a great number of offspring afflicted with vertigo; those who cover several will have fewer. Finally, it is probable that those left alone, without rivals, in a sufficiently large flock will sire none at all.5

So, scrapie would seem to result from sexual frustration among rams.

The veterinarian Roche-Lubin, who practiced at Saint-Affrique in the Languedoc region of France, had a different view, of which he wrote in 1848:

In our land, the causes of scrapie are excessive copulation by rams; the rough fighting in which they engage amongst themselves; the sustained use of feeds that arouse them; leaping; violent exertion; rapid running when being chased by dogs; loud thunder; bright sunshine in the first few days after shearing; and the frequent recurrence of heat among infertile [females].

Furthermore, scrapie is sometimes observed following difficult births; following aborted pregnancies in the first stage of gestation; after recovery or during convalescence from certain intestinal inflammations; after excision of mammary tissue in cases of gangrenous mastitis. . . .
I have never seen a case of scrapie without the existence of one of those causes, which undoubtedly modify, to a greater or lesser extent, the situation by acting slowly or less slowly, but in stages, on the nervous system.\(^5\)

Today, that analysis seems laughable. Perhaps most surprising is the lack of points of comparison—control groups. Indeed, what sheep has never been exposed to one or another of the many causes identified by Roche-Lubin—for example being chased by a dog or hearing a thunderclap? Yet not all sheep have scrapie. We can see from Roche-Lubin’s findings how scientists of the day could draw conclusions on the basis not of properly conducted experimentation but of their own preconceived ideas and beliefs. The central role assigned to the sex life of rams—viewed as frustrated by some and as excessively lustful by others—inevitably reflected the writers’ moral or religious beliefs.

In 1848, the very year that Roche-Lubin published his observations on scrapie, a paper was submitted to the Académie des Sciences, titled “On the Possible Relationship between Crystalline Form and Chemical Composition, and on the Cause of Rotational Polarization.”\(^7\) This was the first publication of a man whose work would revolutionize the approach taken in both human and veterinary medicine: Louis Pasteur. He never so much as mentioned scrapie in any of his writings, but his work would provide the conceptual framework for study of that disease to this day. The work of Pasteur and his disciples, which we shall discuss in the next chapter, finally made possible the truly scientific investigation of the causes of scrapie.
PASTEUR'S EARLY WORK related to what we now call physical chemistry. Before Pasteur, chemists had established that substances—solids, liquids, and gases alike—were in general composed of molecules, which were in turn composed of atoms. A so-called pure substance contains molecules of a single kind, each containing a particular number of atoms linked by very specific bonds. As Antoine Lavoisier (1743–1794) demonstrated in his work during 1783–1785, for example, a molecule of water consists of one oxygen atom and two hydrogen atoms. However, in studying a compound somewhat more complex than water—tartrate, which is deposited in fermentation vats—Pasteur concluded that a molecule is not always completely defined by the atoms it contains and the bonds that link them; their spatial arrangement within the molecule is also a factor. Thus, tartrate could exist in two forms, corresponding to two kinds of molecules each containing the same atoms; each of the two kinds of molecules would be asymmetrical in itself but symmetrical vis-à-vis the other, like our left and right hands.

The asymmetry of these molecules gave rise to a specific, easily measured optical property of tartrate solutions: rotation of the plane of polarization of light. By measuring this effect, Pasteur observed that many
compounds were, like tartrate, composed of asymmetrical molecules, and that all of these were of either plant or animal origin. In retrospect that observation makes sense, because the asymmetry that Pasteur observed was a result of very specific properties of the carbon atom, which is present in all organic molecules—that is, molecules produced by living things. For Pasteur, asymmetry became the hallmark of life, and it was this belief that would draw him to the study of fermentation and then of infectious disease.

Fermentation had been known since antiquity and was used to make bread, wine, and many other foods and beverages. But at the time Pasteur began to study the subject, views of fermentation were greatly confused. Since the invention of the microscope in the late seventeenth century it had been observed that microscopic creatures—known variously as animalculi, globules, mycdermic vegetables, or yeasts, among other names—were present in media undergoing fermentation. But no one understood the meaning of that phenomenon. Pasteur observed that compounds that caused the plane of polarization to rotate would appear or disappear during the fermentation process. In his view these compounds must be either produced or consumed by living things, leading him to conclude that fermentation resulted from the development and multiplication of microorganisms present in such media. He showed that these microorganisms could be cultured in defined media, and that it was possible at any time to trigger fermentation by inoculating a medium with such a culture. Moreover, he demonstrated that each type of fermentation corresponded to a specific microorganism. The organism that caused the sugar in grape juice to turn into the alcohol in wine, for example, was not the same as the one that turned wine into vinegar.

Pasteur needed to understand where these microorganisms came from. Many people thought that these microorganisms, which were seen as rudimentary life-forms, simply appeared spontaneously in environments favorable to their development. This was the theory of spontaneous generation. (Let us not forget: It had been only recently that
mice were thought to appear out of nowhere in a laundry basket left lying around in the loft.) Through extremely rigorous experimentation, Pasteur demonstrated that the appearance of microorganisms in a previously sterilized medium could always be explained by introduction of "germs" from outside that medium. Most often, the germs—the microorganisms—were borne on fine dust particles suspended in the air. Pasteur thus undermined the experimental basis of the theory of spontaneous generation.

The focus of investigations into spontaneous generation would soon turn from fermentation to contagious disease. Before Pasteur, many scientists had noted the similarities between the two. Pasteur himself stated this upon demonstrating that there could be no fermentation in grape juice in which the introduction of environmental yeasts had been prevented: "Might it not be permitted to believe, by analogy, that the day will come when easily utilized preventive measures will end these scourges which abruptly afflict and terrify people, such as yellow fever and bubonic plague?"

From that point, Pasteur set out to show that, like fermentation, contagious diseases were caused by microorganisms, and that each sickness had its own germ. His work, and that of Robert Koch (1843–1910) in Germany, laid down the rules for establishing a causal link between a germ and a disease: verifying the presence of the germ in all cases where the pathology existed; isolating the germ in pure culture; and reproducing the disease solely by using that germ. Those rules were initially applied to the study of a veterinary disease, anthrax.

Anthrax—whose name comes from the Greek for "coal" and refers to the very dark color of the sick animals' blood—caused serious damage among populations of sheep and cattle. The work of Pasteur and Koch proved that it was caused by a microorganism, in this case a bacterium known today as Bacillus anthracis. The mechanism of transmission posed problems for Pasteur, however, which deserve our attention because they are not unrelated to very timely issues related to the mad cow crisis. We shall return to these in Chapter 3.
Through his work on anthrax and a number of other veterinary diseases, Pasteur showed that it was possible to prepare vaccines against those diseases by "attenuating," or weakening, the germs that caused them. He grew anthrax bacteria in controlled conditions and thus obtained a germ that, when an animal was inoculated with it (when the germ was introduced into the animal’s system) would make that animal resistant to the virulent form of the bacillus. The development of an anthrax vaccine had a considerable impact, but doubts remained about Pasteur's theories. In a bid to convince the skeptics, Pasteur turned his attention to rabies, which affected humans as well as animals. Its symptoms in human patients gave rise to a certain fascination, as expressed by one of Pasteur's biographers: "Rabies stirs our imagination. It evokes images of legend and of frenzied patients terrorizing all those around them, tied up and screaming—or suffocated between two mattresses." For Pasteur, conquering rabies would prove his theories once and for all.

But first he had to identify the germ that caused it (and his procedures would provide a model for the study of scrapie some years later). Pasteur began by noting that rabies was transmitted by biting, so perhaps the germ would be found in saliva. Under his microscope, Pasteur examined the saliva of rabid dogs. He saw microbes, to be sure, but he saw the same ones in the saliva of healthy dogs, so that was not the answer. Well, if rabies affected the nervous system, perhaps the microbe might be found there. Here again, the microscope could not detect a rabies germ. But healthy animals would develop rabies if their brains were injected with saliva from rabid dogs or with ground brain tissue from dogs that had died of rabies. And their saliva or brain tissue could, in turn, cause rabies in other animals, and so on. This suggested that the invisible microbe multiplied whenever it passed into another animal; had it been an inanimate poison, it would quickly be diluted through successive generations and would become ineffective. Pasteur was able, in a way, to grow this microbe in the nervous system of living animals, but he was unable to do the same in any culture medium, so the mysterious rabies germ remained elusive. That did not prevent Pasteur, how-
ever, from making a vaccine from the spinal cords of rabbits inoculated with the disease. This was his final great triumph, which won him universal glory and the title of benefactor of mankind. But that is another story.

What, then, was this microbe that was invisible to the microscope but that caused rabies? The key was not found until the early twentieth century. At the turn of that century, it began to be understood that some microbes were so small that they could pass through filters that would hold back the usual kind of germs, such as those of anthrax, plague, and cholera. These ultramicroscopic microbes were called viruses, a name that had previously been very loosely used to cover anything that transmitted diseases but whose nature was not known. Viruses could not be seen with optical microscopes, but the invention of the electron microscope in 1933 made it possible to observe them. Only then could we finally "discover" the rabies virus that Pasteur had used—even though he was never able to see it himself—to prepare his vaccine half a century earlier.