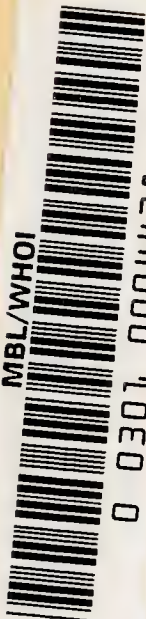




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LOUIS PASTEUR

(1822-1895)

(From a bronze by Theodore Riviere.)



# PASTEUR

## THE HISTORY OF A MIND

*BY*

ÉMILE DUCLAUX

Late Member of the Institute of France  
Professor at the Sorbonne and Director  
of the Pasteur Institute

*TRANSLATED BY*

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*ILLUSTRATED*

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ÉMILE DUCLAUX

(About 1897)

(From a photograph by Paul Rives, Paris.)



## INTRODUCTION

This book is more than a critique of Pasteur. It is a contribution to the biological history of a swiftly changing time, a very striking period in the development of science. As such it should be of interest to all biologists, and especially to all teachers and students of biology and of medicine. For them it was written, and translated. In this time of world upheaval and readjustment, when our young men are looking more and more to France for moral and intellectual ideals, it seems peculiarly apropos that the scientific life of one of her greatest sons, to whom the whole world owes an enormous debt of gratitude, should be set before them clearly and interestingly.

This life of Pasteur was published in 1896, and its author has been dead fifteen years. The book speaks for itself, but in giving to the public an English edition it seems fitting to say some words respecting its author: "*Cette grande et belle intelligence, si simple et si robuste*" (Youriévitche).

The senior translator still remembers with what unexpected and keen pleasure a dozen years ago he saw the title of this book in a German catalogue of second-hand books. For some unexplained reason he had never come across the book in any library or seen any notice of it in any review, nor could he find any of his fellows who had read it, or seen it, or even heard of it. Once, only, since then has he seen it mentioned in a catalogue of second-hand books. Indeed, it seems almost as if it must have died still-born, so little notice has been taken of it, at least outside of France. Duclaux's name was enough, however, and it was ordered straightway, with the fear, oft renewed during the next few weeks, that like many a

coveted treasure mentioned in old-book catalogues, it would be snapped up by another and never delight his eyes. But such was not to be the case. In due time it came (pages uncut) and then what keen delight was his as he devoured page after page, marveling more and more at the wonderful breadth and perspicacity of the presentation. Pasteur seemed alive in its pages, and Duclaux not less alive. No book about a scientific man ever interested him more, or could be written, it seemed, with a more appreciative and discriminating touch. When the last page was finished nothing was more natural, therefore, than to write on its margin: "The most useful book I have read in a long time."

Going over these pages ten years later, the writer sees no reason for modifying his first judgment. The next impulse was to lend the book, and then to wish that it might reach thousands of readers in a suitable English dress. This idea disturbed his spirit so much that finally he began a translation, dictating to a stenographer in the odd minutes of a busy life. Later, it seemed better to turn over a part of this work to an assistant. Eventually, about two-thirds of the rough draft from the French was made by Florence Hedges. We then worked it over together into its present English shape, but those who can read it in the French are advised to do so, since, do the best we could, Duclaux's wonderful idiomatic style has lost somewhat in the translation.

If Pasteur be an incomparable genius, Duclaux, at least, is his Boswell, but he is more than a mere Boswell tagging around after a great man. He is himself a great man. He has a genius of his own which burns with a very clear flame—a genius that penetrates and illuminates whatever it touches, and this has made him an incomparable biographer, and one of an unusual kind. He is no blind partisan or patriot. He thinks his own thoughts,

goes the shortest way to the heart of a subject, and impresses one everywhere as honest and fair in his scientific criticisms. He is an ideal man of science and, moreover, he has what many lack, a direct, forcible, and delightful way of putting things. One would like to know more about such a man, and Madame Duclaux in her interesting book ("I like it best of all the books I have written," she said) has opened the way. In the spirit of her happy motto *Transire benefaciendo*, and mostly from this heart book,<sup>1</sup> I have compiled the following facts respecting the author of "*Pasteur: Histoire d'un Esprit.*"

Duclaux was Auvergnaise. He was born in 1840 in Aurillac in Cantal. Aurillac is a quaint, gray-stuccoed, red-roofed town on a high plateau in the old volcanic region of southern France. It is in a smiling, pastoral country, overlooked by the great rounded flanks of the extinct volcanoes. It is in latitude 45°, due south of Paris 442 kilometers, and north of the eastern Pyrenees 275 kilometers. East and west it lies about midway between Bordeaux and the Rhone at Valence. Already the population begins to be southern in its speech and its manners.

On both sides Duclaux was descended from the great middle class of France. His father was a clerk with wandering and scholarly proclivities, a dreamy and silent man. His mother was a good-natured, joyous, affectionate country girl, the daughter of a small proprietor and merchant. He was the first child. From his earliest days he was brought up very strictly. His father, Pierre-Justin Duclaux, gave nearly his whole time to his education, himself teaching him at first, and later, when he was under other instructors, going over all his lessons

<sup>1</sup> La vie de Émile Duclaux, Par Madame Émile Duclaux (Mary Robinson). Laval. L. Barnécoud and Cie Imprimeurs. 1906. 12mo, pp. 332.

with him. Émile was the apple of his eye; on him was lavished all his interest, rather to the neglect of the other children who were allowed to play as they would while Émile must stick to his lessons, to become the scholar of the family. In this respect the father was a second James Mill or Étienne Pascal. "Sometimes, Mamma, taking pity, sent to inquire after the young recluse. The little brothers entered the study softly and waited religiously until they were spoken to. Sometimes they found the scrivener drawing up a legal paper, but more often they saw him seated at the work-table of his son explaining to him some old author. The opportune moment come, the children clasped the knees of the father and, while he stroked their heads with a distracted hand, he said: 'You have come for Émile? but he cannot go yet. Especially do not talk!' And the lesson went on and on, until the two lads, desperate, withdrew on tiptoe, leaving the elder to his endless task." \* \* \* \* "Father dreamy, incommunicative; mother sensitive and lively. Such without doubt is an excellent combination for the production of a superior man. Such at least were the parents of Louis Pasteur and such those of Ernest Renan."

From his father he inherited a character of rare elevation, an absolute sincerity, and a spirit at once perspicacious and free, a little inclined to criticise, which made him so "generous" in the sense of Descartes; but it was from his mother, the amiable Agnes Farges, that he inherited that overflowing goodness, the openness of mind which he blended with so fine a sagacity, the bantering good nature, always tender so that it did not wound. What he had of skillful and prudent in his character came also from his mother.

The child loved his two parents equally, confided all his thoughts to his father and drew the sweetness of life

from contact with his mother. In return for a devotion without bounds, the father exacted implicit obedience and the son never disobeyed him. If he felt at times the constraint, which made of him an infant prodigy at the expense of his liberty, he never mentioned it, but spoke often of his father and always with tenderness and veneration.

He entered college at Aurillac, where, in 1852, he carried off the first prize for Spanish, as one might expect from a son whose father had wandered much in Spain. Every evening he read some pages of Don Quixote with his father, who was the authorized translator for the law courts. Through all his college studies the father kept pace with him, rising at 4 or 5 o'clock in the morning to study over Émile's college lessons. Again in the evenings, the supper finished, the father and son climbed up to the study, lighted the 3-wick lamp, the antique *lūn*, and began the evening's lessons. Once the lessons were well learned, they read some good author from the treasure of old books the scrivener kept in his little library. There were some volumes of the *Magasin Pittoresque* from which Émile drew his first notions of science, the Letters of Madame de Sévigné, the Memoirs of Saint-Simon, the plays of Racine, a volume of travels in Spain, a little history in two volumes of the Romans in Gaul, and the like.

While he made excellent progress in his classical studies, he was fortunate in falling under the influence of a good teacher of mathematics and the sciences. Especially in Balard's pupil, Émile Appert, who was at the same time chemist, physicist and geologist, and who knew everything and how to teach everything and turned the boy's mind readily from the classics to science, he found just the friend he needed.

Studies over, father and son, inseparable still, rambled

over woods and fields, mountains and valleys. Together they discussed rural things and the old volcanic lands. Émile collected pebbles and explained to his father limestone and basalt, and together they read M. Appert's summaries. The neighbors saw them pass: the father tall, erect and stern, with energetic, wrinkled features, the son meager and little, always holding on to his father's arm, hitching up to be on a level, talking as they went along. "What can they find to talk about so much? It must be they are going to fish for crabs in the valley of the Condamine?"

Such was the boyhood of this man. Between his father and his dear M. Appert he early learned to love nature and especially to look below the surface of things.

The supreme desire of the father was to see his son enter a polytechnic school and become an engineer or an officer of artillery. To enter a polytechnic more preparation was required than could be obtained at Aurillac. Clermont-Ferrand and Toulouse were considered but it was finally decided that he should go to Paris, although it wrung the father's heart to be parted from him. Here he studied under a certain M. Barbet, who predicted for him a brilliant future and was always holding up to him as a model a certain Louis Pasteur, a graduate twenty years earlier from the same institution and the pride of the school, who had just left the faculty of Lille to take charge of the scientific studies of the Normal School in Paris.

For his pocket money at this time Duclaux had 50 francs a trimester. Out of this meager sum in the spring of 1858 he took 35 francs for lessons in diction and for drawing instruments, and for his nostalgia ordered an English book, Scrope's *Extinct Volcanoes of Central France*, which to his astonishment cost him another 30 francs and required dire economies but, in the delight of possession, was worth much more than it cost.

In 1859 Duclaux successfully passed entrance examinations for both the Polytechnic School and the Normal School, and M. Barbet had sufficient influence to cause him to be sent to the latter.

At the age of 19, therefore, Duclaux entered the Normal School and came under the teachings of Louis Pasteur. The father, meanwhile, had died. Each anniversary of the father's death the young man went to pass with his mother in Aurillac. But another bond had sprung up—an enthusiastic respect for the man of genius who was now sub-director of scientific studies in the Normal School. After Duclaux, father and son, it was Pasteur and Duclaux. From the beginning Duclaux ranged himself under his banner and experienced to the depths an influence which modified his whole mind and thought, as it was later to overturn all science. The chemists of the Normal School of 1860 believed in Pasteur as the romanticists of 1830 believed in Victor Hugo, and these are the two great Gallic names of the 19th century. When Duclaux received his degree from the Normal School in 1862 he entered the laboratory as assistant to the master, assistant in a double sense, since the authorities had not appointed any other assistant to sweep up the dust or to wash the glassware. But as Duclaux said later in his charming article on the laboratory of Pasteur which he contributed to the book on *Le Centenaire de l'École normale*, "It is, moreover, a useful apprenticeship for a young scientific man to keep things clean. I will add, although it is perhaps a vanity to be condemned, that I believe I have never had flasks as meticulously cleaned as in that far off time when I cleaned them myself."

Madame Duclaux has drawn a very pleasing picture of him as he was at this time:

"I possess a photograph taken at this period which

shows him very young, slender and alert, with the supple figure of a mountaineer. He is rather small, he has very delicate members, especially his hands, which seem to think. His manner of walking is full of a self-restrained alacrity. His head is large with a good cranial capacity, finely formed, bristling with dark brown hair cut close and planted low and tufted around a perpendicular forehead which is ample but not high. The mask is a little melancholy, elongated as in portraits of the sixteenth century. In this thin visage there are fine eyes, very blue, by turns dreamy, teasing, tender or profound but always limpid. If the eyes suggest poetry, the long nose stands for sagacity and goodness, although the fleshy end trembles in moments of impatience. Fine ears, elongated at the tip like those of a faun, give to this grave oval head of the thinker a delicately rustic character. Already he had the air which I loved so much, a modest, ardent and good expression. Something of the harsh accent of Cantal still vibrated in his voice in spite of the lessons in diction taken at the Institution Barbet and at the Normal School. 'Say *terr*rine, Duclaux,' Madame Pasteur will often say to him, laughingly. The young man spoke well and sometimes copiously, with charm and spirit, but of his personal ideas he was not very communicative, being timid as well as independent. He gave, however, an impression of joyousness when one looked at him, going and coming from one piece of apparatus to another, humming some arietta of Mozart or the refrain of a popular song heard in the street."

At this time Pasteur worked in very cramped quarters in the rue d'Ulm. From such quarters, hardly fit for a rabbit hutch, as Duclaux said, started the movement which was to revolutionize science. Here in the Normal School Duclaux was lodged, fed and received as compensation 47 fr.-50 per month. But what are wages



when one can be with a master! Raulin was his predecessor, a ferocious anti-clerical. Mascart and Gernez were also assistants in the Normal School at this time and friends of Duclaux, especially the latter.

These were the heroic times of the Pasteurian struggle. The master was in the forefront of the debate on crystals, the campaign on fermentations and the great battle over spontaneous generations.

In October, 1865, Duclaux left Paris for Tours, where he had been appointed professor of chemistry in the secondary school. He now had the maintenance of the family on his hands. He was the youngest professor in the faculty of France, being only 26. From Tours he was soon transferred to a better place at Clermont-Ferrand, where a portion of his time could be given to Pasteur's work. When Duclaux was seeking this transfer Gernez interested himself in behalf of his friend and was very much surprised and chagrined one day to learn that he had himself been appointed to the place. This appointment he would not accept nor would Duclaux, under the circumstances, until Pasteur smoothed things out by taking Gernez with him to Alais, which left Duclaux free to accept the position at Clermont-Ferrand, a fine old city, former capital of Auvergne and the birth-place of Blaise Pascal.

At Clermont he had about a hundred students, mostly medical students. The pick of these he admitted to his own laboratory and initiated into the experimental method. Sundays he went with these choice spirits on long excursions through the volcanic lands. His most distinguished pupil was Émile Roux, the present director of the Pasteur Institute, who says, "During these hours of life in the open air Duclaux was the most delightful of companions, overflowing with a deep spontaneous gaiety. The day ended around the hospitable table of

Mamma Duclaux in the apartment in the rue Montlosier. It was truly good fortune for a beginner in science to meet a master like Duclaux." In connection with Roux, as beginner in chemistry, we have the following story. Duclaux had given out a pinch of some salt for analysis. "What is it, my friend?" and the test made, the young man replied, "Sir, I think it is sulfate of copper." "Ah, you think so? Truly? Eh, well, do it over again." At the end of some hours, the pupil returns, "Sir, I believe it is sulfate of copper." "Begin again, my friend." But the third time he returns with indignation in his eyes and voice a little vibrant as he says: "Sir, *it is* sulfate of copper." "So it is, my friend, but you see in chemistry it is necessary to know, not merely to believe or to think."

From Clermont-Ferrand, Duclaux went to Lyons, where he remained five years as professor of physics, and then to Paris (1878) as professor of meteorology in the Agronomic Institute. Through all of these changes it was bio-chemistry which held the first place in his affections, but he was geologist, physicist, meteorologist, agronomist, and chemist, as well as learned in medicine, in brewing and in the dairy industries. He loved to contemplate one aspect of the universe as well as another. To his friend M. Voigt he writes at this time from one of his summer vacations in Fau. "I like the solitude where I live so well that I imagine it ought to have as much charm for my friends. I find myself particularly happy in the country. Free labor and not at all pressing, an independent life, very few books, almost no journals, see how I regain possession of myself."

At another time he wrote: "I am strongly attached to the soil. I communicate with it. I think how many generations of my fathers have lived in contact with it and I take pleasure in asking it about them. I never

come across a wall of big dry stones, a retaining wall made to gain a few inches of earth, an irrigation ditch, an old tree sensing decrepitude, a big rock in a field, without thinking of all those who have builded and planted and dug, or grumbled at having to pass around the rock they could not remove. With such ideas and impressions, there is no solitude. I live in communion with my own, and with this soil, on which they have left the powerful impression of their feeble intelligences and their vigorous arms."

At Paris he displayed incredible activity—mornings and evenings at his work-table and the rest of the day either at the Agronomic Institute or at the Sorbonne (Roux). These were sad years and labor was an opiate. He overworked and suffered from insomnia and for two years from boils. During this time he wrote "*Ferments et Maladies*" (1882) which he dedicated to his wife who had died of puerperal fever. "To you, innocent victim of the infinitely little, I dedicate this book in which I have attempted to popularize their history. May it, slight as it is, serve to hasten a little the day wherein the accomplishment of her sacred mission will no longer cause the wife to fail her husband, and the mother the new-born child." The book made a sensation and a gold medal was struck for it by the Society of Agriculture; also a number of medical men were won over to a belief in microbes.

Duclaux loved to ripen a project for a long time in his mind and to work it over and over on paper before finally putting it into type, which is the secret of all good expression. This was Tennyson's method and Renan's. It was Beethoven's way in music. It is also the method of Anatole France.

In 1882, apropos of "*Ferments et maladies*" which had just appeared, he wrote to his friend, M. Voigt, "You

are very amiable to say so many good things about my book \* \* \* but physicians are those I would wish to lay hold of and I begin to believe that I shall not succeed! I know very well that old physicians do not read any more, and when they do read do not understand. I know that students think only of their examinations, when they think at all; but among the population of hospital internes or externes and that of physicians who have not yet obtained a clientele, I thought I should find attentive readers possessed of good will. Experience begins to demonstrate that I shall not have them." Again he writes: "When I read one of those byzantine discussions of the Academy of Medicine always I ask myself whether the speakers do not wish to understand or simply cannot understand." In 1885 his book "*Le Microbe et la Maladie*" was completed and was published the following year. This year he writes, "My dear friend, Medicine is a strange terrain. It is an edifice where nothing remains standing. Tradition still maintains the plan and general arrangement, but it would be best that everything should come down, because there is no good to be derived from what exists except from the materials. If I were a physician I believe I should give the mattock blow which would make all crumble. Since my manuscript is finished I have become more intimately aware of the fragility of medical notions even those in appearance best founded. Who knows? Perhaps a section of wall will blow up somewhere and a little light penetrate through the opening thus made."

From 1877 to 1896 Duclaux's time was largely devoted to a profound study of milk and dairy products. These studies led him to attribute a preponderating rôle to microbes in all the industries based upon milk. His work in Cantal led to a revolution in cheesemaking and to a great extension of the industry, due to the better

keeping qualities of the properly made cheeses. "The work of Duclaux inaugurated the scientific era in the dairy industry" (Dr. Roux). In recognition of the importance of these researches the Agricultural Society awarded him its great gold medal in 1881.

Duclaux was also the first to gather together and coördinate the scattered facts on the enzymes. This he did in 1877 for Dr. Dechambre's "*Dictionnaire des sciences médicales*." Some pages sufficed at this time, but in 1899 when he took up the subject again for the second volume of his "*Traité*," seven hundred and fifty pages were insufficient. "He returned to this subject many times, showing how the same microscopic organism secretes different enzymes, according to the food that is given it. He classed the enzymes by the reactions they cause and proposed the terminology adopted to-day" (Dr. Roux).

He also devoted much time to the purity of water supplies and to analyzing, especially during vacations in the latter part of his life, the water of springs issuing from the volcanic lands, and said that he could tell whether the water had percolated over limestone or basalt.

Also toward the close of his life he became greatly interested in community welfare, attended conferences, presided at meetings, made addresses, and wrote the charming book "*L'hygiène sociale*."

In 1888 when the Pasteur Institute was founded the workers in the rue d'Ulm had only to transport their microscopes and their balances to rue Dutot, but there was need of someone not to make discoveries, all could do that, but to disseminate them and to formulate a body of doctrines. Duclaux was selected for this purpose. The other colleagues of this time were Chamberland, Roux, Nocard; Perdrix, assistant professor; Loir and Fernbach,

assistants; Grancher, Chantemesse, and Charrin, physicians in charge of the antirabic inoculations; and Eugene Viala, devoted assistant in the rabies service. Also a little later Metchnikoff and Yersen formed part of the staff, but Strauss had gone earlier to a chair in the Medical School. Pasteur was now 66, and the sole shadow on the picture was the ill health of the master. If Pasteur had not been weakened by his second attack of paralysis in 1887, the new Institute might have been very different from what it is to-day, namely, a great coöperative research institution drawing the brightest minds from all parts of France and all quarters of the globe. It might have been greater, at first, but on the death of the master all would have crumbled. Its present form, so cohesive while at the same time so well adapted to maintain the independence of the workers, corresponds rather to the ideas of the collaborators than to those of Pasteur and is due largely to the administrative genius of Duclaux on whom fell nearly the whole burden of the organization. Duclaux wished to make it an immense college of international biology, whereas Pasteur's idea was rather to make it a place where he would work behind closed doors with rare and devoted assistants, not explaining too fully the reason for his demands but being, like an Indian god, one head with many hands. Our good English poet has said:

"The old order changeth, yielding place to new  
And God fulfils himself in many ways,  
Lest one good custom should corrupt the world."

So it was to be here. The old master, the founder, was not always in perfect accord with his friend. Duclaux wished to open all the doors, call the faithful from all corners of the earth, work in a large way, found a scientific college for the future, where each one would be free

while laboring in a common cause. The professor and the social apostle dominated in him. Pasteur was especially a discoverer. Original, profound and slow, he was made to walk alone. He said "we must seek." His disciple added "we must organize and convince." Roux understood both points of view, went from one to the other, and effected a reconciliation, for each one maintained his own ideas only in the interest of the foundation. And so the years passed on, each year giving more and more into Duclaux's shaping hand, until the Institute became such as we see it to-day.

"To this great foundation Pasteur bequeathed a scientific tradition but it was Duclaux who created its soul" (Bloch).<sup>1</sup>

One of Duclaux's first efforts, begun even before the Institute was opened, was the founding of a journal which should be a worthy exponent of the new ideas. Thus came into being in 1887 "*Les Annales de l'Institut Pasteur*," which has done so much for the advancement of human and comparative pathology, and to which Duclaux devoted all of his energy and ability. In this journal, the first volume of which was organized around the doctrine of immunity, he realized an old dream of Raulin, his comrade of other days.

In many ways Duclaux's interests deepened and diversified in these years. In 1888 he became a member of the Academy of Sciences, in the section of rural economy. In 1890 he entered the National Society of Agriculture. In 1894 he was elected a free member of the Academy of Medicine. And always there were his *Annales*.

"My journal (1892) gives me twice as much work since it threatens to become twice as large as at the beginning. I have two laboratories to conduct with two categories of students. In short I am driven: *O rus quando te aspiciam!*"

<sup>1</sup> Annuaire de l'Association des anciens élèves de l'École Normale.

Pasteur died September 28, 1895, and the Council of the Institute elected Duclaux to be his successor. Nothing less resembled the dreamy, intuitive nature of Pasteur, turn by turn combative and silent, than the modest, passionate, devoted soul of his apostle. They were equal only in a generous ardor of soul and in the patient tenacity which both gave to the service of science. Nevertheless, it was Duclaux of all the Pasteurians, who possessed most fully the entire tradition of the master, since he had been more or less closely associated with him and familiar with his ideas since 1858.

Nothing was more natural therefore than that he should write a book on Pasteur. Even before the Institute was thought of, Duclaux wished to erect in his own way another monument to the memory of his master. For he realized how fragile is life and that already many things had ceased to exist except in his memory. Therefore, he wrote this book: "*Pasteur: Histoire d'un Esprit.*" In it the Pasteurian discoveries unfold in their harmonious development with, perhaps, a little more amplitude and coherence, a little less originality and vivid profundity than in the reality. He who has read this book will understand the reach of the greatest scientific movement in the nineteenth century, and at the same time will appreciate how slowly the truth unfolds and how often genius itself loses the thread of the labyrinth in traversing it for the first time. Now that we have made of this daedalus one of the boulevards of the modern mind, it is good to recall what obstacles and what errors then rendered it almost impracticable. The one who knew best the founder of microbiology has written of the book as follows: "After having read this analysis of his work, we understand Pasteur better, and find him greater still" (Dr. Roux). We understand better both Pasteur and Duclaux. Pasteur followed his idea as the magi their



star. "He was a priest; priest of the idea," said his successor. In him, instinct or rather bold intuition, dominated reason. "Therefore," says Duclaux, "he saw with a new vision and justly." His disdain for traditional knowledge and philosophical speculations was scarcely concealed. Trusting only in experiments, he knew how to outstrip them and more than once went far beyond them. "That which puts him outside of comparison is the fact that he loved great horizons, knew how to discover them and to make himself a part of them; that he saw at a distance and through the mists, more clearly than anyone else, the high summit he must attain to dominate the unknown and promised land. This was his rare gift and the secret of his power. But once seen he had wings to reach it, no more than we. One might believe, considering the originality, the simplicity and the unexpected in his solutions, that they were spontaneous and in the nature of happy discoveries. I do not know whether there ever are any such easy discoveries, accomplished without effort and by a sort of divination. Such surely was not the case with Pasteur's. If he was a discoverer it was first of all because he was a silent man and an obstinate one."<sup>1</sup>

Duclaux's spirit was patient and methodical but much less concentrated than Pasteur's. He discovered relatively little, but he excelled in understanding, observing and comparing. Without pride, he loved obscure labor—the only means that permits a great soul, unknown of the multitude, to enjoy liberty and to enter into the delights of meditation. There was something of Montaigne in the vast and varied intelligence of Duclaux. It made no difference to him whether a doctrine or a theory was true, if it incited to labor and led to the discovery of new facts. He made use of criticism and

<sup>1</sup> Duclaux. Discours aux étudiants de Paris. 18 juin. 1896.

hypothesis to interest and to arouse, as an electric current to stimulate the too often inert substance of the human brain. He said: *Je voudrais voir tout marcher autour de moi du même train que moi.* In his "*Discours aux étudiants*" he has expressed himself also as follows:

"The free disinterested search for truth is useful, in and of itself, from the delight it brings to the one who follows it, from the independence of spirit it begets, from the deep sentiment it develops of liberty and of responsibility. I dare maintain even for this inner work that it has no need of looking to or obtaining the suffrages of other men. It is sufficient that we have the consciousness of being in our place and of doing our duty honestly. 'Live,' said Pasteur, 'in the serene peace of the laboratories and the libraries.' I am sure of remaining faithful to his thought in adding: You will not always find glory there, you will never find fortune there, but you will experience there the delight of every day being something more than the day before, and of having brought into the world your share of the truth."

"Do not take my word for things but be enamored of independence," he said. "The fruitful periods of science are those in which dogmas are taken."

"You esteem me too highly," he writes. "There are a hundred thousand Frenchmen who are as important as I am. I differ from them only in that I have been helped more by science. We must distinguish between those who have rare qualities and those who march in the ranks with common qualities, made productive by will and labor."

The national instruction, he said, reflecting on the war of 1870, is not only insufficient but false. Based on rhetoric and on classical studies, it ornaments the mind, but does not strengthen it much; rather we may say it weakens it, since it instills the principle of authority,

and makes all rest on the example of others, whereas youth should be accustomed to see, to scrutinize, and to feel for itself, aided to draw much from its own deeps, and set in quest not of elegance, not of poetry, but of truth. A method of teaching founded on science, preaching examination and research, not recoiling from the minutiae of analysis; seeking in all things to know the causes and the consequences, leaving nothing to chance, cultivating in its protégés prudence and initiative, such a teaching he thought would give to France a new existence.

“I have tried on the children the effect of abstract reasonings (1886). Alas, they do not comprehend them, and, if other children resemble them, the teaching of the exact sciences in the lower grades is very chimerical. They want the concrete, always the concrete.”

He addressed himself to their understanding and their conscience more often than to their memory. “In an old volume of Montaigne at Olmet I found the two fine chapters on ‘l’Institution des Enfants’ full of penciled markings. Such an education, free, strong and healthy, seemed to him well adapted to furnish those two solid foundations of character—independence and sincerity. But to this ideal of Montaigne he added what had been the ruling principle of his own existence; forgetfulness of self and the capacity of devoting himself to a high end. To be a free man; to look in all things beyond selfish interests; to love the truth and to speak it; to act conformably to what seems just; to be mutually helpful. These, unless I am deceived, were his five commandments.”

His ideas on many subjects are full of interest: “It is precisely because science is never sure of anything that it always advances.”

“For the idea of specificity, still dominant ten years ago when I wrote the first edition of my “*Traité de Micro-*

*biologie*" has been substituted another, which is developed in my present book, that of cellular toleration."

"Besides, how is it possible not to see that the immense edifice on which we all labor changes constantly in plan and in foundations. We have lovingly hewn, dressed and even sculptured our stone, with the thought that it will remain perhaps a stone of the façade, and attract the attention of visitors. Vain hope, new tiers of masonry will cover it and cause it to be forgotten. It matters not! It exists, and, if we have chosen it wisely and built it solidly, it will serve as the foundation of new discoveries" (*Discours aux étudiants*).

Propos of the Dreyfus affair, in which he sided with Dreyfus, took public action and suffered correspondingly, he writes:

"We also have rules, which have descended to us from Bacon and Descartes—not to lose our heads, not to put ourselves in a cave in order to see better, to believe that probabilities do not count, that a hundred perhapses are not worth a single certainty. Then, when we have sought and believe that we have found the decisive proof, even when we have succeeded in making it accepted, we are resigned in advance to see it become invalidated by a process of revision over which often we ourselves preside."

"In all this we are very far from the Dreyfus affair; and truly we have a right to ask if the State does not waste its money on educational establishments, the public spirit is so far from scientific." \* \* \*

"If Dreyfus is on Devil's Island, it is only because the Government has listened to the cries of the mob and joined the majority instead of listening to the minority, alone capable of imposing silence on the human brute."

"It has a tragic grandeur. Can you think of a like drama, played by a nation, with that freedom of the

press which allows the whole people to take part in the drama? It is two tragic choruses berating each other. And the scene is France, and the theater, the world."

"The minister was long and diffuse. It is incredible how much this cursed French language allows one to speak without saying anything. There are a certain number of words which straightway show the intellectual poverty of those who use them. Ten times yesterday [at the unveiling in Lille of a monument to Pasteur] the rigid logic of Pasteur was mentioned. But, good people! logic is a proof of mediocrity, and savants who have only logic are not scientific men!"

"Nature loves diversity, education aims at repressing it. Those who later break through into life, show originality and make a name for themselves, are recruited chiefly from those who have escaped the sterilizing influences of the first years."

"*Toute douleur est bonne si elle sert à nous agrandir l'âme.*"

"On peut rêver une humanité supérieure à celle qui s'incarne temporairement en nous."

"Soyons chacun soi-même, soyons différent mais soyons unis."

"Ce que la cellule vivante faisait, sans conviction ni libre arbitre, il était digne de l'homme de le faire, dans l'intérêt commun."

"There is no end to science. So long as there shall be men, there will be savants, and so long as there shall be savants there will be discoveries. Gradually the spirit of men of science has been enlarged and has become open to the idea that the world is immense, that the forces which circulate in it are also immense in number, that those of which we are ignorant considerably exceed those we know. We are sure, from certain examples, that there are circulating around us incessantly count-

less forces of which we are ignorant<sup>1</sup> and will remain ignorant for a long time, things with which other beings than ourselves may be perfectly familiar; for it is here that we find that imperfection of our senses which does not allow us to draw conclusions from ourselves as to other beings which surround us.

“Do not defend yourself against faith and confidence. Life would be an immense dupery, the world in the midst of which we exist would be a colossal absurdity, if the earth were the only abiding place and if what is best in us and among us, should be lost in universal nothingness. The heavens teach not only the glory of God, they teach also hope to all those who are worthy of hope.”

Madame Duclaux closes her account of Duclaux with these words in which many of us will concur: “*L'âme la plus modeste, la plus désintéressée, et une des plus justes de ce temps.*”

The following translation, which I have made from the eulogy on Duclaux, published in the *Annales de l'Institut Pasteur* for May, 1904, and written, it is said, by Dr. Roux, his former student and his successor as director of the Pasteur Institute, will serve as a fitting close to this introduction:

“Once more the Pasteur Institute is in mourning. The third of this month died Émile Duclaux, the director of this Institute, the founder of these *Annales*.

“In less than a year, Nocard and Duclaux have been taken from us!

“All those who have frequented the Pasteur Institute

<sup>1</sup> How right he was must now be apparent to every one. Since these thoughts were expressed in 1901 has come most of our knowledge of the radio-active substances—uranium, ionium, radium, actinium, thorium and their emanations—and all of those revolutionary ideas on the nature of electricity, the structure of matter and the constitution of the universe, which now fill the minds of scientific men with awe and wonder.

will understand our deep sorrow, for they know the sentiments which united the workers of this institution to its director. They were the sentiments of confidence, respect and affection which a true chief inspires.

“After Pasteur, no one knew better than Duclaux how to direct this Institute, where are gathered together young scientific men whose independence he knew how to respect while directing their efforts toward a common end. His authority was beloved, for it proceeded, not from his position but from the qualities of his mind and his heart. One went to him when he felt lost in the obscurities of a scientific research, one went to him also when he felt oppressed by the miseries of life. Confidence was born from the beginning, so cordial was his welcome, so much the luminous glance of his merry blue eye expressed goodness. Duclaux soon learned what you expected of him; his clear intelligence overcame the obstacle which arrested you and his good heart always found wherewith to comfort you. He never lost an occasion to be obliging. On leaving him one always felt stronger for scientific struggles as well as for moral struggles.

“The conversation of Duclaux, simple, full of imagery, full of original ideas, was charming; it was moreover beneficent, because it allowed a character of rare beauty to show through. Thus, this man so jealous of his independence, so respectful of that of others, became, without suspecting it, a director of consciences. None of us, disciples or friends, would have had a tranquil spirit if Duclaux had disapproved any of his actions.

“Duclaux owed this influence to the fact that his acts were worth even more than his words. When he believed a thing just, nothing would have prevented him from undertaking it. He went ahead without blowing a trumpet, without considering the prejudices that would

be overturned any more than the blows that would be received. He was one of those rare men who support a cause, not for the advantages they expect to receive, but simply because they believe it is just. Duclaux supported those which he had adopted with the tenacity of his Auvergnaise blood and also with a force of thought and clarity, and a generous joyousness which rendered his faith contagious. As to attacks against himself, he bore them with an imperturbable serenity; this scientific man with a slender body and frail members possessed true courage, and he possessed it to the degree of giving it to others in tragic moments.

“Goodness and the disinterested worship of justice and of truth were the rules of his private life as they were of his scientific life. It was a delight to him to find in a memoir new facts and well-conducted experiments. If the publication was that of a young man his joy was complete. He showed this in his articles in the *Annales*, which were marvels of exposition and of criticism. So much so, that the author often found in the analyses of Duclaux more than he had himself put into the original.

“In order to make the labors of a beginner useful, Duclaux did not hesitate before the disagreeable task of retouching the manuscript, pruning it, sometimes even rewriting it, in order that the interesting point might stand forth clearly, which point was not always that one which the author had believed.

“His penetrating and just criticisms, with an original and piquant turn, never wounded; they guided into the right pathway and kept from vanity.

“Correspondents from all countries sought the advice of Duclaux and he passed a good part of his time in intercourse with them. He excelled in discovering young talents and in giving to them a knowledge of themselves. He was truly a midwife of minds for he knew how to



bring into the light of day that which was good in the most confused conceptions.

“Duclaux was, above all things, an independent. He esteemed scientific doctrines according to their fecundity without believing them final and thought usually that the fruitful periods of science are those wherein dogmas are shaken. His knowledge was truly encyclopædic; Duclaux had studied to the bottom the mathematical and physical sciences and was quick to understand all the others. Thus he was capable of writing a book like his *Traité de Microbiologie*, and of treating with competence subjects pertaining to physics and to medicine. The readers of these *Annales* have had the proof many times in the critical reviews where he developed a question with remarkable precision and ease. I need not recall to them the qualities of Duclaux the writer. No scientific man of his time has written better than he, no one has better employed his talent.

“Duclaux was an incomparable professor. His facility of speech never served to mask the difficulties of a subject; he went to the bottom of things without fatiguing the attention, because with him everything became easy to understand. His lectures have determined more than one vocation and provoked numerous investigations. He sowed ideas and rejoiced to see them germinate in the fields of others.

“The regrets inspired by the loss of such a man will be extinguished only with those who have known him. But the esteem and the admiration for Duclaux will be durable, for his works will be there to attest that he was a scientific man of the first order and, what is much more rare, a noble character.”

I have ventured to add to the book a few footnotes indicating progress in certain fields of research, an index,

an annotated list of persons mentioned, a portrait of Pasteur made from a bronze in my possession, several from middle-period photographs and one from a photograph taken in his old age. To these I have added two portraits of Duclaux, one from a photograph made a year or two after he became director of the Pasteur Institute (about 1897), the other from an admirable oil painting made by Ernest Bordes in the last year of his life and purchased by the French Government for the Pasteur Institute, both through the courtesy of Madame Duclaux. For a third portrait of Duclaux the reader may consult the Frontispiece in "*Bacteria in Relation to Plant Diseases*," Vol. I, Carnegie Institution of Washington, 1905, where also may be found another portrait of Pasteur and one of Roux.

The greatest progress of bacteriology since this book was written has been in the field that would have interested Pasteur most, namely, in that of immunology, which now has its own text-books and journals. Read in the light of the new knowledge, the Eighth Part of this book seems very ancient history although it well expresses the current ideas of twenty years ago and will always serve as an important landmark.

E. F. S.





ÉMILE DUCLAUX

(From a painting made during the last year of his life, by Ernest Bordes.)

## AUTHOR'S PREFACE

On opening this volume someone will say: "How is it possible to make the history of a mind? One could write an exact history of a man: he has spoken, he has written, he has done things; we know where to lay hold of him, and can follow him and judge him. But a mind, especially that of a scientific man, is a bird on the wing; we see it only when it alights, or when it takes flight. When it is the mind of a genius, like Pasteur, the difficulty seems almost insoluble. We may, by watching closely, keep it in view, and point out just where it touches the earth. But why does it alight here and not there? Why has it taken this direction and not that in its flight toward new discoveries? If it were possible for you to know this and tell us, Pasteur would no longer be a genius, escaping analysis; and if you do not tell us, you will merely draw up a report, not write a history."

All this is true, and nevertheless I have written this book. I have done so for two reasons: the first is that Pasteur was not a savant like the others. His scientific life had an admirable unity; it was the logical and harmonious development of one and the same thought. Of course he did not know when he made his first studies in crystallography that he would end by discovering a means of preventing rabies. But neither did Christopher Columbus know when he set forth, that he would discover America. He only divined that by going always in the same direction he would find something new. So with Pasteur. From the beginning of his studies he had before him a problem of life, and, having found the road to it, from that time he always traveled in the same direction, consulting the same compass. Without doubt

he has traversed many different countries leaving footprints, but he did not intend to explore them; they were merely along his pathway and the grandeur of his discoveries makes it possible for the history of his mind, even though reduced to a report, to clothe these adventures with all the air of a romance.

My second reason is that in its details this scientific life is no less interesting than in its ensemble. As one may readily conceive, Pasteur encountered many difficulties and many obstacles. These obstacles we recognize more clearly as such, now that they have been surmounted and we see them behind us. It is interesting to see how Pasteur outflanked or evaded them. He employed for that purpose qualities of the first order. At the same time audacious and prudent, deceiving himself sometimes even for a long period but being brought back constantly to the true path by that exacting experimental method of which he has so often spoken gratefully, he is always worthy of admiration and worthy also to serve as an example. It is less for the purpose of making an eulogy than for purposes of instruction that I have attempted to write his history, in which I set aside all that relates to the man, that I may speak only of the savant. I have desired, in the ensemble as well as in the particulars, to give the genesis of his discoveries, believing that he has nothing to lose by this analysis, and that we have much to gain. But I found the task difficult. It is now for the skeptical reader to say whether I have succeeded.

PASTEUR:  
THE HISTORY OF A MIND









PASTEUR  
(At Thirty.)

# PASTEUR: THE HISTORY OF A MIND

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## FIRST PART

### WORKS ON CRYSTALLOGRAPHY

#### I

#### THE PREDECESSORS OF PASTEUR: HAÜY, WEISS, DELAFOSSÉ

If we wish to take exact account of the progress brought about in science by the different studies of Pasteur, the first thing to do is to become acquainted with the state of our knowledge up to the time when each one of these studies advanced it. In order to understand clearly the progress they have made, we must know from what they started. But that is not as easy as we might think. To get an idea of the general intellectual status of any period one must not content himself with reading the classical books and manuals of the epoch: these books are always behind the knowledge of the laboratories, that which is in the air, that which one breathes, and which arouses investigators. We encounter another danger in resorting to sources and original memoirs; viz., the danger of taking the opinions and ideas of their authors for current opinions and ideas. A scientific man worthy of the name is always in advance of his contemporaries: between him and them is a middle zone in which one must take his stand in order to judge the undertakings and the progress of a period; but where is one to find this middle ground, and how, when he has found it,

is he to see justly, that is to say, to judge with the judgment of that time? How abstract oneself from what has been learned since, and take on again the necessary ignorance?

Nevertheless, I shall attempt to do this throughout this volume; but, as it is easy to understand, the greatest difficulties are at the beginning. Familiar as we are to-day with the theories of molecular structure, we have some difficulty in picturing to ourselves the chaotic condition of these ideas among the scientific men of 1840.

They had a knowledge of the chemical molecule. They knew it is formed by a grouping of generally quite stable atoms, the number, weight and nature of which are ordinarily very well defined. They knew, for example, that there is one atom of chlorine and one of sodium in marine salt, while in calcium carbonate there is one atom of calcium, one atom of carbon, and three atoms of oxygen. They had recognized that the different compound molecules differentiated themselves ordinarily by the number and nature of the atoms composing them; that there are, nevertheless, some which contain the same number of the same atoms without being identical, from which one was led to suppose that they were arranged somewhat differently. But in what did these arrangements consist? How do the atoms dispose themselves in relation to each other in a molecule? What is the resultant form for this molecule? These were questions on which no one had clear ideas.

Crystallography had given no answer, contrary to what we might believe to-day, after the teachings which this science has furnished us. It held to Haüy's narrow and geometrical conception of the *integral crystal molecule*. We know that he called by this name the little solid, the juxtaposition and superposition of which in an infinite number resulted in the formation of the crystal.

By breaking a cubic crystal of marine salt we reduce it to many little cubes which, pulverized in their turn, would bring us, if it were possible to push the division far enough, to the integral molecule, which also we may suppose to be a cube. By superposing, or placing in juxtaposition a sufficiently large number of these invisible cubes we can form a cubic crystal of any volume whatever, and this example suffices very well to represent to us the integral molecule of Haüy. But, in the mind of this savant, these integral molecules of the crystal bore no necessary relation to the chemical molecule. In order to make an integral molecule of marine salt it sufficed that eight chemical molecules, each formed

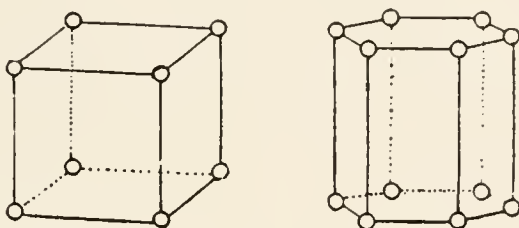


FIG. 1.—Diagrams illustrating primitive conceptions of the distribution of molecules in crystals.

of one atom of chlorine and one of sodium, should group themselves into the form of a cube. What these chemical molecules, themselves, might be, spheres (as represented in Fig. 1), cubes, tetrahedrons, etc., was a matter of entire indifference; their form had nothing to do with it; it was their grouping alone that determined the form of the integral molecule of the crystal and, consequently, that of the crystal itself.

This grouping, according to Haüy, was determined by the particular nature of the chemical molecule and could only occur among molecules which were similar and completely identical. The geometrical regularity was evidence of the physical and chemical regularity. The discovery of facts relating to isomorphism came

shortly to change ideas on this point. By showing that without changing the form of a crystal of calcium carbonate, Iceland spar for example, it was possible to replace as large a number as one wished of atoms of calcium by an equal number of atoms of magnesium, Mitscherlich introduced, in a form still vague, a structural conception of the crystal entirely different from that of Haüy. If atoms of calcium and magnesium can, without any change of form, be substituted one for the other in a crystal, it is because they are of the same form, or what amounts to the same thing, because they act at a distance in the same way. Thus the geometry of the integral molecule was abandoned to approach the geometry of the chemical molecule, and one could say that calcium, magnesium, iron, manganese, and zinc, which give carbonates crystallizing in the same form as Iceland spar, have atoms of the same form, while barium and strontium, which give entirely different carbonates, not isomorphic with the first, have atoms of another form. As in the molecules of the carbonates of calcium, of iron, of magnesium, of manganese and of zinc everything is identical (except the metals, whose atoms are of the same form), it was assumed that the chemical molecules of these different bodies are also of the same form, and by conceiving that the integral molecules of the different crystals are also of the same form, the conclusion was reached that between the crystalline form of any substance whatsoever and the constitution of its chemical molecule a relation existed which, though still vague, was most certainly much closer than the theory of Haüy assumed it to be.

Clearly not all of these deductions were based on solid foundations, and one could almost as well have explained these new facts on the doctrine of Haüy by admitting that the chemical molecules of different forms could

balance themselves at the eight angles of a cube, and that a molecule of carbonate of iron could displace without disturbance at one of these angles a molecule of calcium carbonate of an entirely different configuration. But a new theory in order to be useful and fruitful does not need to have a solid foundation. It is enough that it should be sufficiently well founded to give a new point of view, one which allows the investigator to see things the other way around, and it even happens that some inexact theories may claim an active part in progress. The progress which the very original researches of Mitscherlich brought about was incontestable.

Some years later, M. Delafosse, a pupil of Haüy, studying another phenomenon than isomorphism, that of the hemihedron, advanced a step farther. The beautiful geometrical laws stated by Haüy were sometimes found lacking. They required, for example, that, since the eight angles of a cube are identical from a physical point of view, every natural modification which acts on the one should also act on the other, for why should there be any choice? If one of them is intersected by a plane and is truncated, this truncation, whatever it is, must be repeated eight times. But it sometimes happens that only four of the angles of a cube bear planes, and these are placed in such a way that no two of them are ever at the extremities of the same edge of the cube. The ensemble of these four faces prolonged in the imagination form a tetrahedron. This is the case with boracite which crystallizes in the cubic system. Quartz likewise forms hexagonal prisms (Fig. 1) and the twelve angles at its two bases are physically identical. Nevertheless, it often happens that only six of these angles, situated for example alternately above and below the lateral edges, are intersected by facets which, joined together, would form a rhombohedron with six faces.

One finds analogous facts in the other systems of crystals. Whence come these apparent exceptions to that regularity which, really without knowing just why, we attribute to the laws of nature?

Haüy was very familiar with these phenomena of the hemihedron and if he did not attribute to them any great importance it is because his theory led him to a somewhat distorted view of them, as I have just said. According to his conception the form of the integral molecule was, first of all, that which cleavage, the natural division of the crystal, gave to it. A cubical crystal of marine salt produces cubes by cleavage; a rhombohedral crystal of Iceland spar gives in the same way rhombohedrons. The rhombohedron was, therefore, for Haüy a primitive form. When we intersect the six lateral angles by planes having the same angle of inclination to the faces of the rhombohedron, we obtain by a perfectly regular process of derivation, the hexagonal prism of quartz. And so for the other cases. This conception formed a logical and coherent whole, but left Haüy indifferent to the questions of the hemihedron.

In order to understand the hemihedral character of the rhombohedron, it is necessary to reverse the order and take the hexagonal prism as the primitive form. Then the rhombohedron can be derived from it only by way of the hemihedron. The same is true in the other systems. Weiss, the mineralogist, did this and straightway the hemihedron appeared to be a phenomenon more frequent than was supposed, and there arose a problem requiring solution. Why this deviation from the law of symmetry?

This is what Delafosse tried to explain in 1840, by the aid of a deceptive hypothesis which to-day seems very childish. "In the prismatic quartz," he said, "the hemihedral constitution exists without being



visible externally, since this prism can be derived from a rhombohedron. Some rhombohedrons may, very easily, pile themselves up in such a way that they form a hexagonal prism. In the same way some tetrahedrons may so adjust themselves as to give a cube. Therefore, if we admit that the crystalline net-work of prismatic quartz is formed of rhombohedral molecules, as boracite is formed of tetrahedral crystals, all difficulty vanishes between Weiss and Haüy: the molecular polyhedron will express the dissymmetry by its form, but this dissymmetry will not necessarily appear in the external aspect of the crystal."

This solution of the difficulty is, I repeat it, very infantile. It is a pure invention and Delafosse did nothing to give it a firmer foundation; nevertheless it made for progress, by virtue of that which I have just pointed out, for it introduced into the mind this idea that the form of the integral molecule of the crystal is not as closely bound up as Haüy thought with the form of the crystal itself. We shall soon see the influence of this conception upon Pasteur, the pupil of Delafosse, and, like him, passionately fond of questions of molecular structure.

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## II

### BIOT AND J. HERSCHEL

The general law, just now stated, that a science progresses above all by changing its point of view, explains the aid which it always derives from kindred sciences; and it is especially because young minds search most eagerly and are more open to these suggestions from without, that youth is particularly the time when the spirit of invention flourishes. In the case with which

we are dealing the progress came by way of physics from the introduction into the questions of mineralogy of the power to rotate the plane of polarization.

We know that every impression of light is the result of a vibration. It is as though a rigid rod, clamped in a vise at one end, should vibrate at the other end, oscillating about a position of equilibrium. If, on the moving end, there is a polished button making a luminous point, we can describe with this luminous point an ellipse, a circle, or a straight line. Let us consider this last case, the simplest one, and let us call, for sake of argument, the plane of polarization the plane which contains the vibrating rod and the luminous line which its extremity describes. Let us suppose this plane vertical, and the luminous point moving before us in the line occupied by the hands of a clock indicating six o'clock, i.e., in a vertical line. As long as only the air intervenes between the luminous point and our eye the vibration will not change direction, but there are many transparent substances which, when traversed by the vibration, would make it project itself along the lines of the hands of a clock indicating five minutes of five for a certain thickness traversed, or ten minutes of four for a thickness twice as great. In other words, these substances rotate the plane of polarization to the left an amount proportional to their thickness. We call them substances having a left rotary power, or, to abbreviate, *left-handed substances*. There exist, furthermore, *right-handed substances*, of which, *mutatis mutandis*, the definition is the same.

Crystallized quartz, the hemihedral form of which we have just seen, is typically one of these substances endowed with rotary power; it rotates the plane of polarization of a ray of light which traverses it in the direction of the axis, and Biot, in the very careful study

which he made of the laws of this rotation, remarked that certain quartz crystals, of a definite thickness, rotate the plane of polarization as much to the right as other quartz crystals of the same thickness turn it to the left. He summed up the whole matter briefly by saying that there are *right-handed* and *left-handed* quartz crystals.

But here a curious circumstance presented itself. Haüy had observed at the angles of his prismatic quartz crystals some hemihedral facets ( $x, x'$  Fig. 2) different from those in the simple example which we have just

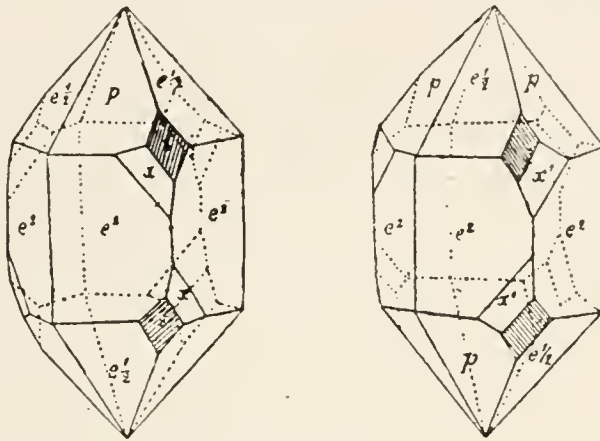


FIG. 2.

Quartz plagi-hedral left.

Quartz plagi-hedral right.

been considering, but which when prolonged would still give a rhombohedron. He had also remarked that these facets, which, in pursuance of symmetry should have been doubled for each of the angles which they cut, were in the majority of cases single, that is to say that only one of them was preserved and this facet inclined according to the crystal, sometimes in one direction sometimes in the other, to the edge which bore it. When the inclination was in one direction with respect to one edge of the prism it was in the same direction with respect to the five other edges. He called *plagi-hedrons* all crystals which had these hemihedral facets; *right-handed plagi-hedrons*, those in which these facets

inclined to the right, the crystal being oriented in a manner agreed upon; *left-handed plagihedrons*, those in which it inclined to the left. There he rested the matter. His pupil, Delafosse, had likewise seen in these crystal-facets only the confirmation of his ideas respecting the tetrahedral character of the integral molecule. If we imagine a series of tetrahedrons, threaded end to end along a rigid rod, this thread will terminate at one end in a point, at the other end in a plane; the one extremity corresponded, for Delafosse, to the corner which was not truncated and remained pointed, the plane surface to the other extremity bearing the hemihedral facet.

For some years the discovery of Biot and that of Haüy existed side by side in science without influencing each other. It was John Herschel who applied to this inert machinery the drop of oil destined to make it go. He bethought himself of combining the purely crystallographical observation of Haüy on the right- and left-handed plagihedrons with the purely physical observation of Biot on the right- and left-handed quartz. Since one defines arbitrarily the crystallographical position of the crystal of quartz which he examines, it is possible to place the crystal in such a way that the right-handed quartz shall be also the right-handed plagihedron, and the left-handed quartz, the left-handed plagihedron. Thus there appeared to be a connection between the crystalline form and the direction of the rotation. Observe that this arbitrary definition which we have just made is not at all obligatory and may be replaced by the opposite one. What is essential is that the existence of the rotary power was put by Herschel into relation with the inequalities in construction of the crystal, and that alongside of the different but nevertheless similar structures which the existence of the right-handed

and left-handed plagihedrons oblige us to admit as present in the quartz, we can place the parallel, but inverse, actions which it has on polarized light.

I have just spoken of structure. It is necessary to make here an important remark: this action on polarized light manifests itself only in crystallized quartz. With the amorphous quartz, or silica in solution in any liquid whatsoever, we no longer find a trace of it. Furthermore, the action takes place only on a ray of polarized light traversing the crystal in the direction of its longer axis and parallel to that axis, or at least in a direction very little inclined away from it. It diminishes rapidly in proportion to the augmentation of the inclination, and there is no longer a trace of it when the ray traverses the crystal obliquely and in the direction of its shorter diameter.

This circumstance, which connected the rotary power with the molecular files of Delafosse, was so much the more curious as it did not occur at all in the other substances in which Biot had also discovered the rotary power. Almost all of these substances were products of animal or vegetable life: sugar, tartaric acid, different essences, albumen, etc. But those which could crystallize, the sugar and the tartaric acid, had no polarizing action in the crystalline state. All, on the contrary, when dissolved in water or any liquid whatsoever, rotated the plane of polarization, some to the right, some to the left. This rotation is always the same for the same solution when the density is the same, regardless of the direction in which the light ray is made to traverse the liquid which is being examined, and we can agitate this liquid during the observation without changing in any way the quantity and direction of the rotation, a fact which well demonstrates that it does not depend on the internal arrangement of the active molecules in the solvent.

This goes to show, and Biot was well aware of this fact, that the action exerted by the solutions of tartaric acid or of sugar is not due, as in quartz, to the arrangement of the molecules in relation to each other, that is to the form of construction, but to the shape of the molecule itself, a form which must be related to its constitution.

It is a considerable stride which this conception forced us to take. It enabled us to attack a question which Haüy had neglected and which Delafosse had scarcely touched—the question of the form of the molecule. It enabled us to see in the arrangement of the atoms of this molecule dissymmetrical dispositions, analogous to that of the integral molecules of the quartz crystal in the arrangement of the crystal. As to the quartz itself, it had awakened ideas, but its importance diminished much in comparison with substances which had the rotary power within the molecule. With the watches in his show-case a watchmaker can make regular geometrical arrangements analogous to some of the crystalline systems; these attract the eye and are subject to certain laws, but as soon as we see that all these watches are going and indicating the same hour we cease to think of the arrangement in the show-case and reflect rather on the movement of the watch. What connection could there be between the arrangement of the atoms in the molecule and the rotary power?

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### III

#### PASTEUR: THE TARTRATES

Such was the question which Pasteur must often have put to himself, for it was at this juncture that he made his appearance. Under Delafosse he had acquired the taste for these researches, and as soon as he was out of

the normal school and able to enter the laboratory as "préparateur," he made ready to pursue them. In order to accustom the eye and the hand to the things with which crystallography deals, he conceived the excellent idea of taking as guide a rather extended treatise on crystalline forms, proposing to repeat all the experiments and all the measurements, and to compare his results with those of the author whom he followed step by step. He chose for this purpose a work by Provostaye on the tartrates, a most fortunate choice, for among the substances endowed with rotary power, the tartrates are those which present in simplest form the phenomena toward which the ambition of the young savant directed him. With other salts he would have been obliged to search much longer to find things not so clear, but he would have found them in the end.

He had, in fact, constantly present in his mind, this correlation between hemihedrism and the rotary power discovered in quartz. It was useless to say that it had no apparent connection with the case of tartaric acid, that is, that it resided in the arrangement of the molecules, instead of in the molecule itself; the ideas of his master as well as his own, reverting constantly to this subject, told him that there ought to be *something* external indicating the mode of arrangement of the atoms. One of the best proofs that he searched for this something which his imagination had glimpsed in the memoirs of Biot and Herschel, is that he saw at once on the crystals of tartaric acid and the tartrates those hemihedral facets which neither Provostaye nor Mitscherlich had observed. The former, a conscientious worker but without inspiration (*sans flamme*), had certainly seen them but he had disregarded them. The second, whose fame is well established, was occupied in his study especially with showing the isomorphism of the tartrates,

which have these facets, and of the paratartrates which do not have them. He could not have much consideration for these hemihedral facets which sometimes upset a parallelism, otherwise so marked. With a slight exaggeration we may say that Mitscherlich did not wish to see them and did not see them, while Pasteur, who wished to see them, saw them at once.

It must be stated, however, that these facets are not always very apparent in all the tartrates and in all the crystals of the same tartrate, but we can ordinarily make them more manifest by changing slightly the conditions of crystallization. In short, as soon as attention is called to them and we search for them, we find them in all of the tartrates.

This confirmed the idea of a correlation between hemihedrism and the rotary power, but this correlation was still remote. In appearance at least not even here was there that correlation between the position of the facet and the direction of rotation which made the right-handed quartz the right-handed plagihedron, and the left-handed quartz the left-handed plagihedron. The crystals of the different tartrates belong to different systems, and have therefore very different aspects, and we do not find that beautiful harmony of forms which makes almost twin brothers of the different prismatic crystals of quartz. The confirmation which Pasteur had just made would have remained fruitless without another discovery to give it the life it still lacked, and if the first discovery belonged to the man of reflection and imagination the latter was due to the experimenter.

I have just said that the crystals of the different tartrates have the most varied aspects; there are needles, tabular crystals, and prisms; they are more or less covered with facets which cut off their angles or their edges and mask their primitive form. But in spite



of the variety of their physiognomy there are some features which remain immutable among them and constitute their family mark. These features are three facets which always succeed each other in the same order and make between them very nearly the same angles. These facets, which consist in the primitive form of two contiguous faces, P and M (Fig. 3), and a facet  $b^1$ , cutting off the intersection of the first two, are parallel to the same straight line which might replace for us that axis of the hexagonal prism of quartz, which has been so useful to us in establishing the correlation between the direction of the hemihedrism and that of the rotary power in this crystal.

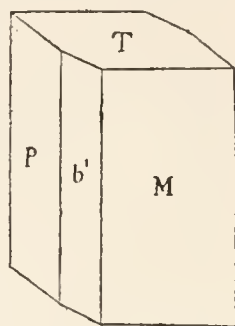


FIG. 3.—Primitive tartrate crystal.

Let us agree to place this right line vertically in our tartrate crystals and to turn forward the group of three facets which is that characteristic the different crystals have in common. All the crystals can thus be ranged, in spite of the variety of their forms, in an oriented series like soldiers exhibiting in front the same series of buttons. But when one has arranged them thus he perceives with surprise that all of these soldiers bear only one epaulet, turned in every case in the same direction: I mean to say that all these tartrates have their hemihedral facet inclined forward to the right of the observer.

If one turns them half-way around they are like children's lead soldiers, or like the god Janus, inasmuch as the front cannot be distinguished from the back: the hemihedral facet from the rear is now in front, but it is always to the right. If one reverses them in order to observe them from the other end they resemble then the double figures on playing cards; their extrem-

ities resemble each other and however one places them, provided that one puts in front the characteristic group of the three faces that we have pointed out, one of their four hemihedral facets comes again obstinately to take up its position facing the observer, and at his right.

Thus, a curious circumstance, all the tartrates so varied in form, which Pasteur had studied to the number of 19, have a rotary power in the same direction, and also a hemihedrism in the same direction. This correlation related them to the quartz but had a deeper meaning, for here it could be no longer a question of arrangement of the molecules in the crystal, but of arrangement of the atoms in the molecule. It is clear that one can change the conventions, for example, examine the crystals on the edge as is the custom in Germany, instead of on the face, as is the custom in France. In that case the hemihedral facets incline to the left when the rotary power remains to the right, but it is the statement of the phenomena which changes, and not its nature: all the tartrates having a rotary power in the same direction have also a hemihedrism in the same direction, and that demonstrates a relation between the form of the molecule and its mode of action on light.

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#### IV

#### THE PARATARTRATES

It is evident that we have made progress since the study on quartz. Now we find ourselves studying with Pasteur the manner of grouping of the atoms. And here belongs an unforeseen discovery.

In the factories where tartaric acid is made one

sometimes finds in the cavities between the large crystals of this acid some little needle-like crystal forming tufts which are visible as an opaque white mass on the surface of the semitransparent tartaric acid and sometimes so much resemble oxalic acid crystals that in the factory of Thann, where they were formerly very abundant, they have been taken for oxalic acid crystals and an attempt made to sell them as such. It was soon recognized that they were formed of a particular kind of tartaric acid, giving salts entirely similar to the tartrates. Mitscherlich, who made a comparative study of the known tartrates and of these new salts, which he called paratartrates, found them identical in all their relations. They had the same crystalline form, the same specific gravity, the same double refraction in the crystalline state, the same angle of the optical axes, the same index of refraction when they were dissolved in the same proportion of water. In short, no method, either physical or chemical, made it possible to distinguish them, and they seemed identical in every respect, save this, that the tartrates acted on polarized light while the paratartrates were entirely without action.

Having arrived at this stage in his researches, Pasteur could not fail to be impressed by this apparent contradiction. "Mitscherlich was deceived," he said, "in affirming that the crystals of the tartrates and the paratartrates resemble each other. There must be some external differences between them as regards the hemihedral facets. Mitscherlich, preoccupied with his ideas on isomorphism which made much of all the crystalline resemblances between the different forms, would not have seen these differences which he did not seek, but I, who have the preconceived idea of their existence, am in a good position to find them if they are there."

Experiment, questioned in this fashion, gave an immediate response. All the paratartrates examined appeared with their two epaulets, that is to say with all the faces required by the laws of symmetry: there was no more hemihedrism: the facet on the right had its corresponding one on the left and, simultaneously, every trace of action on polarized light had disappeared.

This was a confirmation of Pasteur's foresight, a reward of his daring intuition. But, in addition to this foreseen discovery, chance, one of those happy chances which one rarely meets with save when he is constantly in search of it, kept in store an unexpected discovery. Among the paratartrates there were two which behaved differently when they were crystallized. The others gave crystals having hemihedral facets in pairs, and consequently had no hemihedrism, just as he is no longer one-armed who has two arms. On the contrary, the double paratartrates of soda and ammonia on the one hand, of soda and potash on the other, deposit in their mother liquors crystals which are all hemihedrons, all one-armed; only there are some of them which have the right arm, and others the left.

What did this mean? If one regarded these facts as a whole, the result was confusing, since it showed the apparition of hemihedrism where there was no rotary power. But Pasteur had advanced too far to go back. He had already derived too much advantage from his conception to lose confidence. "In spite of all that was unexpected in this result," said he,<sup>1</sup> "I followed none the less my idea. I separated with care the right and left-handed hemihedral crystals and observed separately their solutions in the polarization apparatus. Then, with no less surprise than joy, I saw that the right-

<sup>1</sup> Recherches sur la dissymétrie moléculaire. Leçon professée à la Société chimique de Paris, 1860, p. 29.

handed hemihedral crystals turned to the right and the left-handed ones to the left the plane of polarization, and when I took equal weights of each of these kinds of crystals the mixed solution was neutral to polarized light because of the neutralization of the two equal and opposite individual deviations."

We can understand how in the presence of this unexpected phenomenon, with its almost dazzling confirmation of his preconceived idea, Pasteur received such a shock that he quitted the laboratory, incapable of again applying his eye to the polariscope. This was a clear ray of sunlight coming to illuminate perspectives which he had thus far examined only in shadow or half light. Now that they were suddenly illuminated it was not the time to abandon them.

The more so as immediately there was a harvest to be reaped. In removing chemically from the right-handed hemihedral crystals the tartaric acid which they contained, he found an acid which, when compared minutely with the acid of the grape, was found to be absolutely identical with it. The left-handed crystals furnished him furthermore a tartaric acid also identical in every respect with the acid of the grape, save in one point, that is that it bore on the left the hemihedral facet which the first bore on the right, and that its solutions deviated to the left exactly the same amount as equally concentrated solutions of the tartaric acid of the grape deviated to the right. When these solutions were mixed there was no deviation, and one obtained a third tartaric acid, the paratartaric acid inactive by compensation. Furthermore, this acid did not result from a juxtaposition of these two constituents but from their combination, for properly concentrated solutions of right-handed and of left-handed tartaric acids often give off much heat when mixed, and the liquid solidifies on the spot with an

abundant crystallization of a paratartaric acid identical with the acid of Thann with which we set out.

To summarize, there existed there tartaric acids identical from the point of view of all their physical and chemical properties, save this, that they each had their special hemihedral facets and the corresponding rotary power. These differences persisted in all their compounds and formed a part of their true nature. They formed their distinctive marks, which were permanent and deep.

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## V

### ASPARTATES AND MALATES

This harmonious development from a single fertile idea will become still more thrilling presently when we go back, as we are justified in doing, to the chemical molecule from which comes the initial influence. For the moment we must ask ourselves whether we are here in the presence of a general or an exceptional fact. Do all these different organic substances, which Biot found endowed with rotary power, present hemihedral forms when crystallized? Unfortunately, not many of them give measurable crystals: asparagin and its different derivatives, aspartic acid and malic acid do, however, and Pasteur made haste to study them.<sup>1</sup>

Asparagin was at this time a rare substance. Pasteur was obliged to plant vetch in the garden and cellars of the Academy of Strasbourg. By known processes, from the juice of these plants he extracted the asparagin which he crystallized and which he showed at the same time to be provided with hemihedral facets and endowed with

<sup>1</sup> Mémoire sur les acides aspartique et malique. Ann. de ch. et de phys., 3e p., t. XXXIV.

rotary power. Like the tartaric acid it carries over this last property into its solutions, whether acid or alkaline, but it presents this unforeseen peculiarity of rotating to the left the plane of polarization when it is in a neutral or an alkaline solution, and on the contrary of rotating it to the right, and to a much greater extent, when it is in an acid solution. In no case, however, has it ceased to be asparagin unless the liquid has been heated or the acids or alkalies have been too concentrated, and it is possible by precipitation to recover it with all the old properties. This proved that the rotary power of a substance did not depend on itself alone and that if the existence of this power had any significance for the ideas on which Pasteur had taken his stand, its meaning and importance were contingent and of a secondary order.

I have just said that, in order to leave intact the asparagin on which one is working, it is necessary not to heat the liquids. Boiled with an alkaline solution, it is transformed into aspartic acid. Does this acid keep any of the rotary power of the asparagin? It is too little soluble in water to make it possible to study it in aqueous solutions. In solution in the alkalies it rotates to the left: in chlorhydric or nitric acid it rotates to the right.

Another derivative of asparagin was still more interesting to study; viz., the malic acid which one can obtain from it by action of hyponitric acid. This malic acid accompanies tartaric acid in the grape and therefore should arouse curiosity. Experiment shows that in regard to the rotary power it behaves a little like tartaric acid, and that it sometimes even recalls it so much in its properties that one is tempted to suppose for the two acids origin from a common atomic grouping. Nevertheless, in their ensemble, the phenomena presented by malic acid and the malates are more complicated than those of tartaric acid and the tartrates. In the latter

we have several series of well-ordered crystals in which the correlation between the two hemihedrism and the direction of the rotary power is always clear. In the malates, on the contrary, the inclination of the facets and the direction of the rotation are sometimes contrary, and thus there disappears, apparently at least, this beautiful harmony which had so charmed us in the tartrates.

If Pasteur had commenced with malic acid he would have needed all his perseverance in order to disentangle himself from the midst of so many contradictory facts. But at the point which he had reached his ideas were too well grounded and his experience already too great for him to be astounded by these particular variations in the direction of rotation of the malates. He had discovered quite parallel phenomena in asparagin, which nevertheless remained always the same, and also in the aspartates. He had even found examples of it in the tartrates, for the left-handed calcium tartrate dissolved in chlorhydric acid gives a rotation to the right.

It is under conditions like these, where the judgment is wavering, that the discernment of the scientific man reveals itself. Without being embarrassed by the differences between the malates and the tartrates, he saw and aimed at one thing only, the resemblances which he had perceived and pointed out, and he concluded with a fine tranquillity that if there was a common atomic grouping between the right-handed tartaric acid of the grape and the malic acid of the sorb-tree, there must also occur a common atomic grouping between the left-handed tartaric acid and a malic acid still unknown, which would be the *left* of the malic acid of the sorb-tree. And thus little by little was born in his hands that science of the arrangement of atoms which has since attained so much importance. Wherever he went Pasteur was an initiator.



Before leaving this subject let us point out a last series of facts and conclusions. Tartaric acid and malic acid undergo changes due to the action of heat; the former gives pyrotartaric acid, the second maleic acid and a fumaric acid identical with that which is derived from the fumitory. Is the atomic grouping which gives to the tartaric and malic acids the property of acting on polarized light preserved intact in their derivatives? Experiment shows that this is not the case. All these acids, pyrotartaric, maleic, fumaric, and their salts are inactive. According to Pasteur's interpretation, the molecules of tartaric acid, aspartic acid and malic acid, are dissymmetrical; those of the pyrotartaric, maleic, and fumaric acids are not: the atoms are differently grouped and a new proof is this, that the two tartaric acids, the right- and the left-handed, give only a single pyrotartaric acid.

## VI

## MOLECULAR DISSYMMETRY

The moment has come to pursue more closely than we have hitherto done these ideas of dissymmetry.

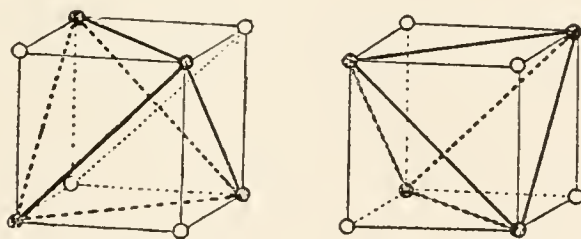


FIG. 4.—Diagrams illustrating molecular dissymmetry.

There is a fundamental difference between the hemihedral forms coming from the cube, as in boracite, or from the hexagonal prism, as in Iceland spar, and the hemihedral forms realized in the tartrates. All the

tetrahedrons which can be derived from a cube by hemihedrism are identical and could fit into one another. The two tetrahedrons represented in Fig. 4, passing through opposite vertices of the cube, have the same angles and edges; it is only necessary to reverse the first in order to make it fit over the second: they are *superposable*, to speak in geometrical parlance. The same thing is true for the different rhombohedrons derived from the hexagonal prism. It is quite otherwise

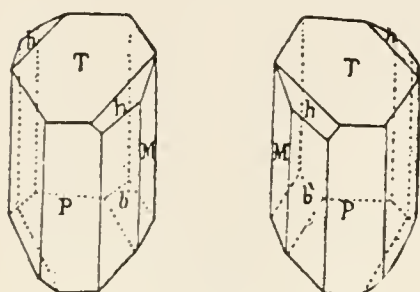


FIG. 5.

Right tartrate.      Left tartrate.

for the hemihedrons of the tartrates. The tetrahedron which one obtains by prolonging and joining the hemihedral facets which a right-handed crystal of tartrate bears, is not superposable on the tetrahedron obtained in the same way from the left-

handed tartrate. Their faces, it is true, are equal two by two, but they are not arranged in the same order in respect to the vertices.

Fundamentally, the difference amounts to this, that the tetrahedron of the cube has several planes of symmetry, to the right and left of which the elements are regularly distributed. If one imagines a reflecting surface passing through any given edge of the tetrahedron and the center of the opposite edge, the image of the rear half in this mirror coincides with that of the forward half, and inversely: in more general terms, the object is superposable on its image in a mirror. We shall say that in this case there is *superposable hemihedrism*. The hemihedrism of the tartrates gives, on the contrary, tetrahedrons which have no plane of symmetry, which are not superposable on their image, and when we reflect upon it we see that "all material

objects, whatever they may be, regarded with respect to their form, or the repetition of their identical parts, resemble the tetrahedrons which we have just distinguished. Some placed before a mirror, give an image which is superposable on them; others do not, although the image reproduces them faithfully in all details. A straight stairway, a branch with opposite leaves, a cube, the human body, all these are objects belonging to the first category. A spiral staircase, a branch with leaves in a spiral, a screw, a hand, an irregular tetrahedron are forms of the second group. These latter have no plane of symmetry."<sup>1</sup>

Of all these comparisons that of the hand is the most

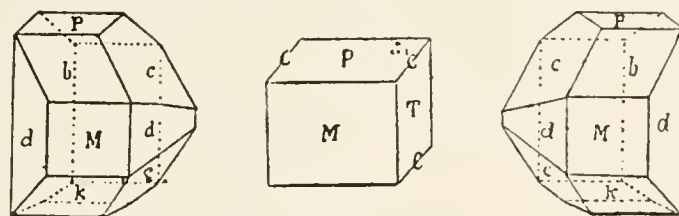


FIG. 6.—Tartaric acids.  
 right. primitive form. left.  
 c. Hemihedral facets.

convenient and striking. The two hands are not superposable and one cannot put the right glove on the left hand, nor inversely. On the contrary the image of a right hand in the mirror gives a left hand. Well! The two hemihedral tetrahedrons of the right- and left-handed tartrates are like the two hands: they are not superposable nor is either superposable on its image, but each of them is superposable on the image of the other in a mirror (Figs. 5 and 6).

Let us recall now that we were led a moment since to attribute forms of dissymmetry connected with the non-superposable hemihedrism of crystals to the

<sup>1</sup> De la dissymétrie moléculaire des produits organiques naturels. Leçon professée devant la Société chimique de Paris, 1860.

arrangement of the atoms in the molecule, and thus we come quite naturally to represent to ourselves the molecules of the two tartaric acids, the right- and the left-handed, not only as dissymmetrical individually and with a non-superposable dissymmetry, but also as having an inverse dissymmetry one with the other. If one is a right hand the other is a left hand. If one is a corkscrew with a *dextrorse* spiral, the other is a corkscrew with a *sinistorse* spiral. In short, we know nothing and we shall know nothing probably for a long time of the mode of arrangement of the atoms in these two molecules, but we remain faithful to logic and the laws of induction in acknowledging that these two arrangements, individually dissymmetrical, are reciprocally symmetrical in relation to a plane.

Once this conception is admitted, we can easily represent to ourselves the effect of these groupings in a water solution on a ray of polarized light which traverses it. Let us suppose that this solution contains only identical and superposable tetrahedrons, for example, those of boracite: these molecules are present in very great numbers in the path of the ray, even when the solution is not of much thickness; they occupy, in the medium in which they are free, all possible positions. Consequently, if we suppose that one of them is inclined in a certain direction with regard to the ray of light and acts on it in a given direction, there will always be another one, identical with it and in the inverse position, which will produce an effect in the opposite direction. The molecular effects will always counterbalance therefore in pairs, that is to say, the light ray will leave the solution just as it entered it, except for the small amount of absorption undergone in traversing it. If, on the contrary, the tetrahedrons in solution are not identical, if they cannot be superposed, it would be

only in very exceptional positions that compensations like those which we have just pointed out could occur, and, without being able to indicate in detail the results or the direction of the general resultant, we see, nevertheless, that the total effect could not be the same as in the first case. The path of the ray of polarized light where the direction of the vibration is constant and unique must depend on the direction in which the obstacles it encounters are placed. Without going into this problem further, it is possible to admit that the deviation of the plane of polarization depends on the manner of distribution of the obstacles, and that, according as the dissymmetry in the atoms is right or left there will be a right or a left rotation.

Of less importance is the mechanism of the action, which always remains a little hypothetical. It is sufficient that the experimental study of the tartrates has linked indissolubly these two ideas: the molecular rotary power, and the dissymmetry of the molecule. This suffices to give us the right to attribute dissymmetrical molecules to all substances acting in solution on polarized light, and when one considers that all these substances belong to the vegetable or animal kingdom, that is to say, are the products of cellular activity, this peculiarity of structure becomes curious, if regarded closely. Guided by an imagination at once so adventurous and so well controlled as was that of Pasteur, we are constantly on the border of new countries, but we journey with security.

## VII

## DISSYMMETRY OF CELLULAR LIFE

The plant, which is the great creator of organic matter on the surface of the globe, is an organism continually engaged in the work of synthesis. By the aid of substances of the highest degree of chemical simplicity, carbonic acid, water and ammonia, it manufactures substances more and more complex, which it stores in the new tissues that it forms according to its needs. As soon as these substances attain a certain degree of complexity we see appearing in them the molecular rotary power, absent up to that time. Carbonic acid, oxalic acid, acetic acid, ammonia, urea and glycol, are without action on polarized light: the sugars, tartaric, malic and citric acids, cellulose, the gums, and the albuminoid substances are active.

At the time when Pasteur made these studies the chemistry of synthesis was still little advanced: Berthelot was just beginning his work. But organic chemistry was in full swing, and inorganic chemistry was leaving the hands of Berzélius and Wöhler to fall into those of Sainte-Claire Deville. Already, at this time, Pasteur was in position to remark that, contrary to the majority of natural organic products, all the artificial products of the laboratories and all the mineral species met with in nature were without action on polarized light, that is to say, they possessed a superposable image. Quartz itself is not an exception, for, as we have seen, it is only the arrangement of the molecules in the crystal which is dissymmetrical. Individually these molecules are without action on polarized light. In the same way one can arrange cubes of wood, which are exactly alike, so as to make a winding and dissymmetrical staircase; there

is dissymmetry of construction but not molecular dissymmetry.

One could put in the same category as quartz other minerals or salts, such as sulphate of magnesium and formate of strontium, substances having crystals with hemihedral facets but the solutions of which are not active. In short, no product of inorganic nature or of the chemistry of the laboratory deviates the plane of polarization of light when in solution; it is only the products of living nature which have this property but they possess it to a very marked degree and carry it with them when they enter into combination with other substances.

Since then, the chemistry of synthesis has made progress, and today, starting, like the plant, with water, carbonic acid and ammonia, and putting into play only the forces and ordinary resources of the laboratory, we are able to manufacture artificially the majority of the natural organic products. Is it necessary, therefore, to change some of the conclusions which Pasteur announced in 1850? Yes, one thing only which he did not foresee. We are able now, by the aid of primitively inactive bodies to manufacture active ones, to thus produce dissymmetry and the rotary power in the molecule which we construct. With inactive succinic acid we can ascend, for example, to tartaric acid. But when a chemist manufactures thus artificially the right-handed tartaric acid he makes also necessarily and simultaneously the left-handed form, so that the combination which comes from his hands is inactive. Nature alone has the secret of manufacturing one without producing the other. In the grape, for example, she gives us commonly the right-handed tartaric acid and not the left, or at least rarely the left, since paratartaric acid, the combination of the right and the left, sufficiently abundant at one time to obstruct the works at Thann, has almost disappeared

there today, as well as from the other tartaric acid factories.

What is the mechanism of this production of a right-handed substance without a trace of the left-handed one, or inversely? Are the two forms produced simultaneously and is one of them utilized and consumed in proportion to its production? In this case nature would behave like a chemist who, after having formed at the same time the two inverse substances, should separate them and cast aside one of them in order to preserve the other. Some facts which we shall soon encounter are in accord with this view. Pasteur adopted another view which, however, is not exclusive of the first. Possessed as he was by this novel idea of dissymmetry, he boldly connected the dissymmetry of natural products with the dissymmetry of their source. The earth is round, it is true, but, he thought, it is only when in a state of repose that it is symmetrical and superposable on itself. As soon as it turns on its axis its image in a glass no longer resembles it, for that turns in a different direction. The sun's rays, which strike and animate a leaf of a plant, no longer have the same direction in the earth and in its image. If there is an electric current circulating in the direction of the equator and presiding over the distribution of magnetism, this current turns also in opposite directions in the earth and its image in the mirror. In short, the earth is a dissymmetrical whole from the point of view of the forces which make it live, it and all that it produces, and it is on this account that, as soon as they have exceeded a certain degree of complexity, the substances which the earth's living creatures produce are dissymmetrical and endowed with a rotary power.

With this idea in mind, Pasteur had tried to crystallize the tartrates in the presence of dissymmetrical forces, for example, the poles of a magnet, and to make a plant



push out shoots by changing the direction of the light rays which struck it. These attempts gave nothing, either to him or to those after him. But it is possible that, repeated with greater persistence and with more powerful means, they would result in something, and that this something would be so remarkable that it would pay for all the trouble taken to produce it. We cannot justly scorn any of these ideas of Pasteur when we see how fruitful have been all those which he pursued.

## VIII

### SUBSTANCES INACTIVE THROUGH LOSS OF DISSYMMETRY

We are going to discover a new proof of the certainty of Pasteur's intuition. Starting with asparagin, and profiting by the labors of Piria, we have seen that we can obtain products more and more simplified: aspartic acid, malic acid, maleic acid, and fumaric acid. In this continued degradation of the asparagin molecule there is a point reached where the molecular dissymmetry disappears, permanently: this is at the maleic or fumaric acid boundary. But it happened in 1850 that M. Dessaignes, an able chemist of Vendôme, succeeded in following inversely the steps of Piria, and of remounting by the chemical path from malic acid to aspartic acid, then, some months later, from fumaric and maleic acids to the same aspartic acid.

The passage from malic acid to aspartic acid had not surprised Pasteur, both of them being active on polarized light, but the case was different with maleic acid. In transforming this into malic or aspartic acid, Dessaignes would have created an active molecule by a laboratory operation. This would have been, in the eyes of Pasteur, a great discovery. He must assure himself of the truth of it at once.

Pasteur, therefore, hastened to Vendôme to state his scruples to Dessaignes, and obtained from him without difficulty a sample of the new aspartic acid which he made haste to study. As he had expected, he did not find any rotary power: this acid was an inactive acid. But it resembled so much, in all its physical and chemical

properties, the acid derived from asparagin, that Des-saignes, who had no preconceived idea to put him on his guard, was very excusable for having confused the two.

This synthetic aspartic acid is especially interesting in that it can be transformed into malic acid by the methods of Piria, and we may well believe that Pasteur was curious to know what malic acid one would obtain with it. Experiment shows that we obtain a malic acid identical with the natural acid, save that it is inactive on polarized light, as are also its salts. This is not all; the field grows more fertile as we cultivate it. The active malic acid of the sorb-tree or of the grape corresponds to one of the active tartaric acids. To what was this new malic acid comparable? To the paratartaric acid inactive by compensation? Pasteur had, against this interpretation, an objection which is no longer valid. "Dessaignes, the father of this malic acid, would," he thought, "in this case have created two molecules endowed with rotary power at the expense of one inactive molecule, but it is impossible to create a single active molecule, to say nothing of two." We know today, not only that the thing is possible, but that it has been realized. It is very probable, if not absolutely demonstrated, that the aspartic acid manufactured by Dessaignes was a combination of the right- and left-handed acids. It is certain that the malic acid which Pasteur had had in his hands was also a paratartaric acid. This error at the outset vitiated the memoir which Pasteur had devoted to comparing the aspartates and malates with each other and with the tartrates. The majority of the deductions which he had drawn from these comparisons are inexact, and must be abandoned. But there are some which survive and which we should note. Even in the early years of his life as savant, Pasteur

always had the good fortune never to wander very far from the right path. His adventurous spirit led him sometimes to the right or to the left of it, as he followed the trail, but he always recovered the true path. It is in these moments when he walked hand in hand with truth that we must lay hold of him: they are the landmarks of his route and of his career.

The theoretical idea which I have just pointed out prevented him from believing that the inactive malic acid was a paratartaric acid. Consequently, it must present a new atomic grouping in which the optical inactivity results not from a compensation between equal and opposed forces but from the disappearance of all dissymmetry in the active molecule. It was very audacious to imagine a new theoretical grouping when there were already three, but Pasteur had audacity and this audacity had often served him well. The malic acid which he studied was not, we have said, the compound with the symmetrical structure, which he had dreamed it to be. Nevertheless he was not absolutely deceived, for this body with a symmetrical structure exists in the tartaric series, as Pasteur himself was to discover a little later.

Here is another point where error did not prevent him from arriving at the truth. Confident in his idea that he had an aspartic acid and a malic acid with a symmetrical molecule not contorted, so to speak, he made a careful comparison of these acids with the twisted and dissymmetrical molecules obtained from asparagin and the fruit of the sorb-tree. He wished to see how this symmetry or dissymmetry of the molecule expressed itself externally, in the physical and chemical characters of the acids and their salts.

From this study he derived no definite knowledge for two reasons. The first is that the substances to which he

turned his attention were not fitted to answer the question asked. But of that Pasteur was unconscious. The second reason, which touched him closely, is that they were contradictory in their responses. The active and inactive aspartates resemble each other very much chemically and sometimes differ entirely from the point of view of crystallography, even to the degree of presenting absolutely incompatible forms, while the active and inactive malates, very similar also as to their chemical composition, are sometimes indistinguishable in a crystalline state. The active and inactive bimalates of ammonia, for example, have the same crystalline form and the same angles. One is often in danger even of taking one for the other, for it happens that the active bimalate does not have hemihedral facets and corresponds exactly in form with the inactive bimalate.

In other words, all the order and harmony observed in the tartrates disappeared, so that not only was Pasteur obliged to abandon without an answer the question which he had put to himself but he might have asked himself anxiously whether in the tartrates he had not accidentally fallen upon an exceptional case, devoid of all general bearing. But no! Not once, it seems, did this doubt cross his mind. At least his writings show no trace of it. From the contradictions which he had observed he concludes with a tranquil assurance that the crystalline form has only a secondary importance, since in the aspartates and the malates it no longer shows the beautiful accord with the optical properties which are so striking in the tartrates. He, therefore, deliberately threw overboard the correlation of the crystalline form with the rotary power, which remains the most certain and most constant evidence of molecular dissymmetry.

Let us pause an instant to observe the successive steps which we have made. Herschel gives us the first idea

of a relation, not only between the existence of a rotary power and a dissymmetry of construction in the quartz crystal, but also between the direction of this power and that of this dissymmetry. Biot shows us subsequently that the rotary power can exist in the molecule. Wherefrom Pasteur concludes that there must be a dissymmetry in the construction of the molecule, that is to say in the arrangement of the atoms. He finds the external indication of this dissymmetry in the tartrates, which serve him, furthermore, to state precisely the meaning of this word dissymmetry, up to that time a little vague. In his mind, then, after his studies on the aspartates and malates, these tartrates become, as did the quartz, merely empty shells, after yielding the idea which they contained. This idea is that of the dissymmetry of the molecular structure and of its constant relation to the rotary power.

There we have the portion of truth which this memoir contains! On reflection the conclusion to which we arrive will appear curious from the philosophical point of view, for here we have a work which had begun by establishing a close relation between the rotary power and the crystalline form, and which ends by scorning this crystalline form. One might think that science had turned about in its place without advancing. But he would be deceived, for here we see clearly how much a matter of indifference it is whether a theory or a doctrine is right, provided that it incites to work, and results in the discovery of new facts. We do not know exactly what is the relation between the molecular structure and the crystalline form, nor even if there is a relation which makes it necessary that they should be subject one to the other. Fundamentally a correlation between the existence of certain crystalline facets and the arrangements of atoms in the molecule, appears to us rather

remote, and therefore as a contingent, but the fact that the idea of this correlation has given us, through Pasteur, the idea of the dissymmetrical structure of the molecule, suffices to make it beneficial, whether false or true.

Here we have, in reality, the idea which has come forth from it quite naturally, like the grain from the ear: a molecule which possesses the rotary power is dissymmetrical. But a dissymmetrical molecule cannot be contained in one plane because this plane would be for it a plane of symmetry. Therefore, the molecule must form in space a geometrical solid of three dimensions. That is the first conclusion. Here is another: as we are familiar with the number and nature of atoms entering into the molecule we may attempt to arrange them in such a way that the dissymmetry of the solid which they form corresponds to the direction of the rotary power of the molecule. Summed up, such is the series of deductions drawn nearly simultaneously in France by Le Bel, in Holland by Van't Hoff, and which have served to found a new science, stereo-chemistry, of which Pasteur is thus the forerunner.

Let us forget, then, all the false interpretations of this memoir on aspartic acid, and note only the certainty with which Pasteur, arrested by a conception, inexact in the case to which he applied it, but the general justness of which the future was to confirm, succeeded in tracing a fourth plan of construction for an active molecule. "We are here," he would have been able to say at this moment, "thanks to the discovery of inactive substances, in possession of a fertile idea. A substance is dissymmetrical, right or left: by certain artifices of isomeric transformations, which must be sought and discovered for each particular case, it can lose its molecular dissymmetry, be twisted, to use a rough comparison, and effect

in the grouping of its atoms an arrangement with a superposable image. Thus each dissymmetrical substance offers four variations or, rather, four distinct sub-species: the right-handed body, the left-handed body, the combination of the right and the left, and the body which is neither right nor left, nor formed by a combination of the two."<sup>1</sup>

I shall dwell no longer on the aspartic and malic acids because, as I have just said, Pasteur had taken the wrong route. This has been evident since, and it is singular that its discovery has required no new methods; it has only been necessary to employ those methods with which he has made us familiar. By following them M. Bremer has shown that the inactive malic acid of Pasteur was in reality a paratartaric acid, that is to say, a combination of right- and left-handed acids. It has been discovered also that there are three asparagins, three aspartic acids, three malic acids, and that the maleic acid and fumaric acid are more distinct than Pasteur believed them, and possess a new dissymmetry which is not expressed by the appearance of a rotary power. In short, our knowledge has been very much extended since Pasteur did his work, but there has been no change in its source, and in its immense development it remains faithful to this parent idea of Pasteur, that all difference in the grouping of the atoms of a molecule must be expressed externally in some way. That Pasteur was sometimes self-deceived, and that there are some defective stones in the foundation which he has given to the edifice, is of no importance. The essential thing is that the edifice rises without crumbling, and that it does rise.

<sup>1</sup> De la dissymétrie moléculaire des produits organiques naturels. Leçon professée devant la Société chimique. 1860.



## IX

## COMBINATIONS BETWEEN ACTIVE MOLECULES

If the ideas which we have just developed have served as a foundation for stereo-chemistry, others in the same group will lead us to the study of fermentations, that is to say, to one of the most beautiful conquests of this century of marvels. For this, let us go back to the study of the tartrates. We have seen that any left-handed tartrate is the twin brother of the corresponding right-handed one. Save that they bear their hemihedral facets in different ways, when they have them, and that they have equal rotary powers but in opposite directions, the two brothers are exactly alike not only in respect to their geometrical form, solubility, density, etc., but also in what one might call the physiognomy of the crystals. These twin crystals are equally limpid or clouded, hard or fragile, polished or striated; they have the same internal fissures, in short, they cannot be distinguished unless one subjects them to a very careful examination. We have taken exact note of these resemblances in order to convince ourselves that the molecules of these crystals are identical in everything save their atomic arrangement. The moment has come to consider this resemblance from another point of view.

Up to this time it has been manifest to us only in the combinations of the right and left tartaric acids, with certain mineral substances: potash, soda, ammonia. Inactive on polarized light, as the minerals are, these substances are content, so to speak, with diluting the active power of the tartaric acid on entering into combination with it. But what happens if one combines these tartaric acids with active substances? If the latter, as is probable, maintain their power in the compound, this

power will be contrary to that of one of the tartrates, and will exalt that of the other. What will be the outcome of this internal conflict on the physical and chemical properties of the compound? It does not seem, *a priori*, that it will be expressed externally in the same way as the harmonious dissymmetry of the tartrates. What does experiment say?

Impelled by this ingenious and original idea, which, let us remark, was, moreover, from the point of view of the history of his mind, a logical consequence of his conceptions, Pasteur tried, in fact, to combine with active malic acid and its compounds, the right- and left-handed tartaric acids and their compounds, asparagin with the two tartaric acids, etc. Between the different substances thus produced he actually determined some differences greater than those existing between the corresponding substances formed by means of inactive bodies. But the results are clearer when one combines the tartaric acids with the organic alkalies of plants, quinine, cinchonine, brucine, strychnine, etc., endowed also with the rotary power. The identity of the chemical properties which existed in the tartrates with mineral bases disappears. The right- and left-handed tartrates of the organic alkalies are no longer either equally soluble or equally hydrated. They bear very unequally the action of heat, and they lose more or less easily their water of crystallization. If by chance their chemical formula is the same their crystalline forms are different and incompatible. Finally, sometimes, with asparagin, for example, combination is possible with the right-handed body, impossible with the left. As for their rotary powers, instead of being equal and opposite, as in the case of the combinations of the tartaric acids with mineral bases, there may be either addition or subtraction, and the resultant deviation is very different in the

right- and left-handed tartrates in combination even with the same organic alkali. In short, we observe some differences which can be attributed legitimately only to the reciprocal influences of the acid and the base in combination.

And, thenceforth, we are authorized to philosophize with Pasteur. It is very probable that all natural, active bodies present, like tartaric acid, at least three forms, the right, the left, and the para. Then when we combine two substances each of which has its right, left and inactive form, it is possible to obtain nine different combinations, identical as far as the number and nature of the atoms is concerned, but different in their arrangements. This difference of arrangement will admit of the addition of an unequal number of molecules of water of crystallization which will be more or less difficult to drive away with heat. It will involve, furthermore, differences in crystalline form, in solubility, and in chemical stability. On the whole, it is sufficient to constitute nine different substances, which number could be increased to sixteen if we take into consideration, in addition to the three forms pointed out above, the form by nature inactive, which Pasteur had not yet discovered in the tartaric acid.

Of a complete series there was no example at the time when Pasteur worked, and I do not know whether there is one to-day. Then, there were only some scattered terms but these permitted the beginning of proof. Precisely the combination of the right-handed tartaric acid with the left appears in the forecasts above made, and it is remarkable that one finds between the tartrates and paratartrates differences of the same order as those which we have just pointed out. The chemical composition is ordinarily not the same, the crystalline forms are incompatible, the solubilities are different, etc.

It is true that this is not always the case, and Pasteur would have been able to find contrary examples in the history of the malates if he had not made the error which we have pointed out above. But, on the whole, one can accept this way of looking at it as sufficiently exact, and Pasteur was right to introduce it into science. The marked differences which one observes between the various sugars encountered in nature, for example between rock candy and its constituent sugars, are evidently of the same order and have the same origin. I will venture to add that it is reasons of the same kind which render so baffling the study of albuminoid substances, in which differences of molecular structure are expressed externally otherwise than by differences in crystallization.

If we now recall that the protoplasm of all living cells is endowed with the rotary power, that it contains, therefore, dissymmetrical molecules, and that this dissymmetry in relation to the stability or instability of the compound, cannot fail to play a rôle in all the chemical combinations of which the protoplasm is the seat, we shall conclude that there are in these considerations indications of a profound mechanism of life. We encounter here one of those flights of imagination which Pasteur permitted himself sometimes and which were for him the recompense and the repose derived from works of research. But when he had thus boldly explored the horizon he made haste to regain the solid ground of experiment. Let us follow his example and enter the laboratory.

## X

## MEANS OF SEPARATING THE RIGHT- AND LEFT-HANDED SUBSTANCES

We have to deduce from the preceding facts one of the consequences which they allow. Now that we have substances of the same composition into the molecule of which we can introduce either an identity, or foreseen and premeditated variations, let us ask ourselves if we cannot impart to the two tartrates, right and left, which precipitate at the same time from a solution of the double paratartrate of soda and ammonia, a difference in solubility great enough so that one will be deposited before the other, when the liquid is left to evaporate. That would be a great advantage. At present, we only know how to separate them by hand, observing individually their hemihedral facets in order to determine how they are placed on the crystal. That demands time, patience, and a profound knowledge of crystalline forms. Furthermore, when deposited, the crystals are generally in a mass, and one is never sure that a right-handed crystal which one detaches from the mass does not bear with it fragments of a left-handed one. The separate crystallization of the two salts would certainly yield them in a much purer state.

Let us search then in this direction, Pasteur surely said, and he soon found, in reality, that in crystallizing the paratartrate of cinchonine, the left-handed tartrate which is less soluble was deposited first, and to such an extent that by decanting at a given moment the mother liquid, and evaporating it anew, there was found in it only the right-handed tartrate. It was a *natural* separation of the two acids, otherwise so similar. I imagine that when Pasteur performed this experiment for the

first time he was no less happy than when he saw the double paratartrate of soda and ammonia break up unexpectedly. That was an unforeseen discovery on his pathway; here, on the other hand, the discovery was searched for and foreseen, which doubled the interest of it. The paratartrate of cinchonine is not, moreover, the only one which lends itself to such a separation: that of quinicine is similar, but in this case it is the right-handed tartrate which is deposited first.

We are, then, in possession of a second means of separating the active components of a paratartaric acid. Let us say immediately that it is by this method that M. Bremer demonstrated the inactive malic acid of Pasteur to be in reality a combination of the right- and the left-handed acids. Let us say, also, that a third means was conceived by M. Gernez in the laboratory of Pasteur. It was incident to the preceding in that the separate crystallization of the two tartrates was provoked, not by differences in solubility, but by a suitable crystalline decoy introduced into the supersaturated solution. With a decoy formed of right-handed tartrate one obtained the crystallization of the right-handed tartrate; with one of the left-handed tartrate, that of the left tartrate. This was, then, under another form, it is true, a dissymmetrical influence introduced to obtain the separation.

Another means discovered by Pasteur is still more curious and introduces us into the realm of life. It had been known for a long time that lime tartrate left to itself under water decomposes with the formation of various products. One day Pasteur observed a solution of right tartrate of ammonia placed in a flask in the laboratory to be decomposing in the same way. The liquid which was at first clear (let us keep this fact in mind because we shall need it later) became clouded

as the result of the development of one of those organisms which invade infusions, and then a drop of this clouded liquid sufficed to induce a fermentation in a new flask.

Thus far nothing surprising: we have before our eyes one of those phenomena of decomposition of organic matter which are constantly taking place around us. But here is where the investigator awakes and the originality begins. For others the fact was commonplace; for Pasteur it was life engaged in a struggle with a compound endowed with rotary power. This form of plant life which grew and developed in the flask was composed of cells giving birth to dissymmetrical products, as do all living cells, and then there presented itself quite naturally and imperatively the following question: how will this organism behave in a solution of paratartrate?

Let us transfer a drop of the fermented liquid of right tartrate of ammonia to a solution of paratartrate of ammonia. Things follow their course, and nothing outwardly distinguishes these two fermentations. But let us study them with a polarization apparatus. Let us filter, at definite intervals, a portion of the solution of paratartrate and pass through it a ray of polarized light, and we shall see that this liquid, inactive in the beginning, has acquired a left rotary power which increases little by little till it reaches a maximum. At this moment fermentation is suspended, the liquid clears, it contains no longer any of the right-handed salt which is the only one the fermentation has attacked and transformed. The left-handed salt has been respected and can be recovered by evaporation.

The phenomena, it is true, do not always proceed in just this manner. Everything depends on the microscopic organism which is sown, and developed, in the liquid. Pasteur has never described the one which he observed; it would seem that he had been working with a

species of *Penicillium*. Since then Pfeffer has found a bacterium which acts like the species studied by Pasteur. On the contrary, a bacterium that developed spontaneously in the laboratory, in a solution of left-handed tartrate of soda and ammonia, consumes by preference the left tartrate from a solution of paratartrate, although it is quite able to attack the right also. Other living species consume indifferently the two salts, and all cases are possible. But we are none the less in possession of this fact: that the nutritive character of a tartrate may bear a relation to its molecular dissymmetry.

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## XI

### GENERAL CONCLUSIONS

This fact merits special attention. The right- and left-handed tartrates of ammonia are composed of exactly the same elements, carbon, hydrogen, oxygen, nitrogen, in the same quantity. The only difference is in the arrangements of the atoms. Still this difference is not great since the two arrangements are the image of each other in the mirror, and nevertheless it is great enough so that a living organism can respect one of the two salts while it entirely destroys the other.

To understand this fact it is evidently necessary to relate it to what we know on the subject of the difference in chemical properties brought about by combination of tartaric acid with an active substance. In the presence of potash and soda the right and left tartaric acids behave exactly alike and have the same stability. This is no longer the case when they unite with substances having rotary power. Now it is just these which they encounter in the living tissues where there are



always active substances though it may be only the albuminoid matter of the protoplasm.

On the other hand, all phenomena of nutrition are protoplasmic, that is to say the food of any cell, whatever that food and whatever the cell, must begin by forming a part of the protoplasm before being consumed or utilized. From this we understand that the two tartrates do not lend themselves with the same facility to this combination, or, that once combined, they have different stabilities. Thus it is that the active bimalate unites with the right-handed bitartrate to give a crystalline combination unrealizable with the left-handed bitartrate. Thus it is that the two tartrates of quinine are quite dissimilarly resistant to the action of heat.

A living cell appears to us, therefore, as a laboratory of dissymmetrical forces, where a dissymmetrical protoplasm acting under the influence of the sun, that is to say, under the influence of dissymmetrical exterior forces, may preside over quite varied actions, may manufacture in its turn new dissymmetrical substances which add to or take away from its power, may utilize one of the elements of a paratartronic acid without touching the other, may manufacture crystallizable sugar at one moment to consume it at another, make reserve foods today and exhaust them tomorrow, in brief, may show the marvelous plasticity which we know to be characteristic of it, and all that very simply, without any stir, by means of very small deviations of forces under dissymmetrical influences.

The nature of the albuminoid substance of each cell, or, to speak more generally, the direction of the dissymmetry of one or several of the elements of its protoplasm, exerts thus on its functions and therefore on its *development*, an influence of the first order, the mechanism of which, obscure up to this time, is a little clearer when

seen in the light of Pasteur's work. What kind of a world would it be in which one would replace the cellulose and albumen in the actually living cells by their opposites and, to recall to our minds that which we have already gone over, what kind of a world would it be in which the earth should turn around the sun in a direction opposite to that which it now takes, an earth where the electric current which makes of it a magnet should take an opposite direction and where the point of the compass needle which marks the north should mark the south?

We are right in thinking that it would be a world not identical with the actual world. We may even believe that it would differ very much, and behold therein the profound thought of Pasteur, the bond which unites our nature to cosmic phenomena. We are all the children of the sun, as someone has said, speaking from another viewpoint. We see here more than that. The sun not only distributes the force, but it influences its direction and its use.

We see also, at the same time, all the difficulty which one would encounter in approaching the problem by experiment. In order to introduce into a cell proximate principles different and opposite from those which exist there, it would be necessary to act upon it at the time of its greatest plasticity, that is, to take the germ cell and try to modify it. But this cell has received from its parents a heredity in the form of one or several active substances, the presence of which is sufficient to render it rebellious to certain actions and to make it accept others, that is to say, to impart to its evolution a definite direction. This cell contains in the beginning not only its *being* but also its *becoming*, and it is therefore an initial force which augments without ceasing by giving its own direction to new forces which appear every day in the little world it governs. *Vires acquirit eundo.*

And the life of the whole results from the sum total of these cellular lives.

Ah! If spontaneous generation were possible! If one could create a living whole, could cause to evolve from inactive mineral matter a living cell, how much easier it would be to give it a direction, to make these foreseen dissymmetries of which we have spoken enter into its substance and thence into its vital manifestations! I am adding something to what Pasteur has written on these captivating questions, but I do not believe that I have gone beyond what was in his thought in my effort to show how the methodical and regular study of the questions which ranged themselves before him, as he advanced, was able to put him in the presence of two of the problems which it was fated that he should solve: the question of fermentations and that of spontaneous generations.







PASTEUR

(From an old Lithograph.)

(Courtesy of Capt. J. C. Pryor, Naval Med. School, Washington,  
D. C.)

## SECOND PART

### LACTIC AND ALCOHOLIC FERMENTATIONS

#### I

#### THE KNOWLEDGE OF FERMENTATIONS BEFORE LAVOISIER

At the time Pasteur approached it, the question of fermentations formed such a confused mass that not only is it difficult to picture to ourselves what the chemists of the epoch thought of it but we doubt even whether they had any clear idea of it, we find so many contradictions and singular statements in their writings. When we seek to discover whence came that embryonic notion respecting fermentation, persistent to the middle of the nineteenth century, we see that it was due not to the difficulties of the subject, but to the fact that the question had been a philosophical one before it became a scientific one.

The phenomena of fermentation are as old as the world, and the first that man learned to control and to adapt to his needs are probably those which lead to the production of bread and wine. More time and effort doubtless was required to procure beer. Once found, it was inevitable that the methods which yielded these articles of food and drink should spread rapidly and soon become common. The bubbling which takes place spontaneously in the mass of vintage, or which is produced in the barley wort by the addition of the yeast of beer, the change of savor and texture which results from the introduction of yeast into the flour paste are

phenomena too curious not to have attracted, from the beginning, the attention of philosophers, who contented themselves with borrowing from them comparisons and figures, and the curiosity of searchers for the philosopher's stone, who were less disinterested. Might not a base metal be transformed into a precious one by means analogous to that which derived a savory bread from an indigestible paste? Is there not some powder of transmutation acting like a ferment? Here we have the question which the alchemists asked themselves and which naturally they did not solve, first because it is insoluble, second because though they were experimenters, they were still more logicians, believing in the power of the idea, and inclined to subordinate experiment to it.

It is not that there do not exist in their writings phrases in which, if one is so inclined, it is possible to see, like the break of day, the forecast of recent discoveries. But in reading these ancient authors we must always bear in mind that the word with them has often preceded the idea because of the general mode of education of the middle ages, and that in the sciences the idea has almost always preceded the fact. The word has no value of its own; an idea, so long as it remains a view of the mind, is always balanced by an opposing idea; the fact alone is convincing and brings certainty. But facts are what the alchemists scarcely ever found on the question of fermentation. The definitions of it which they have given are only obscure or pretentious paraphrases of the phenomena observed in the manufacture of wine or of bread. They make allusions sometimes to the setting free of gas (*exaltatio*), sometimes to the fact that the fermented bread can, in its turn, act as a yeast (*immutatio*). But as they knew nothing of the nature of the substance which ferments, nor of



that of the products of fermentation (save that of alcohol, known for a long time), it is difficult for them to escape glittering generalities.

The honor of having provoked serious studies by showing the worthlessness of the little that was known belongs to Paracelsus (1493–1541). Although of new facts he himself contributed very few, his militant way, his great mind, his disdain for traditions and the philosophical speculations which at that time dominated science, all these brilliant and substantial qualities, could not fail to have a powerful influence on his contemporaries. To the attraction of the studies in themselves he added the allurements of a close personal interest. To him, man was a chemical compound; diseases were caused by some alteration in this compound; the putrid fevers, for example, were due to excremental substances, which instead of being rejected were retained in the economy. Hence, the utility of searching for chemicals which could combat efficaciously these maladies. Paracelsus, we see, might be cited as the forerunner of the theory of antitoxins. The truth in that he argued well, but it was, after all, only argument.

This association between the phenomena of fermentation and disease does not really date from Paracelsus. It influenced his predecessors: it furthermore influenced his successors down to Pasteur, who gave it a precise significance. We find it becoming more and more clearly defined from the beginning of the seventeenth century, which opens the era of work and discovery. It takes an experimental turn with Van Helmont, who discovered carbonic acid in respiration, putrefaction, digestion, and in the fermentation of wine; with Becher, who passed several years in the practice of fermentations and whose writings profited by his long experience. Unfortunately dissertation regained ascendancy with R. Boyle, in other

respects so original, and especially with Stahl, whose influence on his century was so great. His was a high intelligence, a powerful and generalizing mind, but he believed in fencing with words, and was not a scientific man.

He introduced into his theory of fermentation, sustaining them with his great authority, ideas already professed by Willis. According to Stahl, "Every substance in a state of putrefaction easily transmits this state to another body still free from decay. Thus it is that a similar body animated already by an internal movement (let us bear this idea in mind for we shall find it again in Liebig), may, with the greatest facility, involve in the same internal movement another body still in repose but disposed by nature to a similar movement. \* \* \* There are two periods in fermentation thus considered as the result of an internal movement; in the first, the different molecules of the fermenting substances are gently agitated, and some parts, more or less attenuated, gather together; in the second, the parts separate themselves from the mixture as a result of the movement which animates them, and the analogous parts reunite to the exclusion of the others."

According to Stahl, the ferment intervenes only to communicate its movement to the analogous parts of the liquor to be fermented. Its action, therefore, we should say today, is purely dynamic. Let us hasten to remind ourselves once more that we must not read into the phrases of the ancients our modern ideas. The conception of Stahl derives its fundamental origin from two classes of facts, the manufacture of bread and of wine: the first a transformation arrested at its beginning, during which the agitation is feeble and in which the parts in the vicinity of the ferment become fermented in their turn; the second characterized, on the contrary, by a

violent movement, which communicates to the liquid the gas, or *spirit*, which is set free. Adjust these two phenomena, end to end, generalize them, and you have the definition, cited above, of Stahl and his predecessors. If with Stahl it ended in assuming a more definite form, it was because the atomic theories of Descartes had penetrated into chemistry. Save for this addition from without, which appeared rather in the way of stating it than in the idea itself, the theory of Stahl says nothing more than that of Lefèvre and Lémery, and other chemists on the time. It has been said of this theory that it was philosophical and seducing. A theory does not need to be philosophical and seducing; it does not even need to be true in the absolute sense of the word, as we have shown; it suffices that it be fertile. But the theory of Stahl was not fertile.

Progress in the field of fermentation came from without and had for its origin new facts observed in the study of gas by scientific men who were contemporaries of Stahl. Moitrel d'Elément (1719) learned to make gases visible by passing them through water; Hales (1677-1761) showed how to manipulate them; Black (1728-1799), how to distinguish them one from another. He isolated especially carbonic acid, learned to know its properties, and discovered, something which Van Helmont had not been able to do, that, aside from alcohol, it is the sole product of the transformation of sugar in the alcoholic fermentation. He placed thus in the hands of the chemists all the principal elements for the solution of the problem; it remained only to coördinate these elements and to establish their mutual relations: this was the work of Lavoisier.

## II

## FROM LAVOISIER TO GAY-LUSSAC

Here we are able to point out, as we have done with respect to the introduction of polarization into chemistry, the fruitful power of a new instrument entering into a science which had previously not known it or had neglected it. It is to the introduction of the balance into chemistry that Lavoisier owes his glory; it had served him well in the solution of other problems: it solved also the problem of fermentation. Lavoisier placed on the pan of a balance a vessel filled with water to which he had added a given weight of sugar and a little yeast of beer. From the loss of weight undergone by this vessel at the end of the fermentation, he inferred the weight of the carbonic acid<sup>1</sup> liberated during the process of the phenomenon. He then separated the alcohol by distillation, weighed it, and found that the sum of the weights of the alcohol and the carbonic acid gave very nearly the original weight of the sugar. The conclusion is easy to draw: the sugar simply breaks up into alcohol and carbonic acid; there are no other normal products of the transformation.

But there is more than that in the experiment of Lavoisier. The relation which exists between the weight of the sugar on the one hand and that of the alcohol and carbonic acid on the other, ought also to be verified individually for each one of the elements of these bodies. The carbon of the sugar ought, for example, to be found entire in that of the alcohol and the carbonic acid; the same should be true for the hydrogen and the oxygen.

<sup>1</sup> Following the usage of Pasteur and his opponents and all the older writers, this book, which is an interpretation, calls the dissolved gas and the free gas, indifferently, carbonic acid. *Trs.*



PASTEUR  
(At Forty-five.)



It is sufficient, therefore, to know the composition of the sugar, of the alcohol and of the carbonic acid, in order to prepare the balance sheet of the reaction, which Lavoisier sums up in these clear terms: "The results of the vinous fermentation are reduced, therefore, to separating into two portions the sugar which is an oxide, oxidizing one at the expense of the other to form carbonic acid, deoxidizing the other at the expense of the first, to form out of it a combustible substance which is the alcohol, so that, if it were possible to recombine these two substances, the alcohol and the carbonic acid, we should again obtain sugar."

Here, apparently, we have reached a truly scientific ground, and it seems as though, from this point on, progress will be made in great strides. But this problem is unlike others; everything in its course has been uncertain and laborious; it even exhibits this fact, not rare, but always curious, namely, that its progress has been due as much to error as to truth.

The conclusions of Lavoisier were exact but his work was not. Because of the lack of good analytical methods he was deceived in the composition of the sugar employed, and in that of the alcohol produced. And if, in spite of these errors, which should have vitiated everything, he reached a conclusion correct in its general features, it was due entirely to a chance compensation of errors. Happy chance, one might say, providential chance, which has had such enduring and useful consequences!

Useful, for Lavoisier had apparently so clearly explained the mystery of fermentation, had reduced it to a formula so simple, that the idea of this simplicity has never left the minds of scientific men. This became apparent when Gay-Lussac and Thénard, after having perfected the processes of organic analysis, determined the exact composition of cane-sugar. It was then very

easy to be convinced that all Lavoisier's conclusions were overthrown and that the work must be done again or the conclusions revised. But as for Gay-Lussac himself, so convinced was he of the truth of the interpretation of Lavoisier that he contented himself with searching whether the formula of the sugar, as determined by his perfected method, would not accommodate itself so as to break up into alcohol and carbonic acid. This was to admit as exact the short-lived conclusion of Lavoisier. But the proof very nearly succeeded. Believing that Lavoisier was entirely right, Gay-Lussac did not hesitate even to give what is commonly called a *coup de pousse*, and to modify from 2 to 3 per cent the figures which his experiment had given him in order to make them fit into the hypothetical outline traced by Lavoisier. A singular spectacle! the degree of confidence and security of conscience to which a preconceived idea may lead! A strange spectacle to see Gay-Lussac continue, but happily only on this one point, the tradition of those alchemists of the middle ages, who consented, it is true, to inquire of experiment, but who did not question it impartially, and listened only when it answered in accordance with their desires!

Starting from an inexact experiment, supported by the figures of an analysis voluntarily perverted, the idea of Lavoisier nevertheless made its way, because of its simplicity. It naturally met with more credence when Dumas and Boullay observed in 1828 that every incorrect statement in the interpretation of Gay-Lussac could be made to disappear by admitting that the cane-sugar assimilates the elements of a molecule of water before undergoing alcoholic fermentation. This interpretation, supported by experiment, reestablished both the truth of the idea of Lavoisier and the accuracy of the calculations of Gay-Lussac; it had only one thing against



it—it was entirely a work of calculation. It had no other foundation than the experiment of Lavoisier which was evidently not exact, and had not been the object of any verification.

Any one who had wished, about 1850, to get an idea of the degree of credence which the equation merited, the equation of alcoholic fermentation accepted everywhere, would have been justified in being entirely sceptical on the subject, especially if he had asked himself why all the chemists who were occupied with this question passed by obstinately in silence this yeast which Lavoisier had been obliged to add to make his sugar ferment, and without which it was impossible to obtain any fermentation. Why should this yeast, so necessary in the experiment, disappear in its interpretation?

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### III

#### CAGNIARD-LATOUR, SCHWANN, HELMHOLTZ

This yeast was known in the vats of the brewery as a kind of superficial scum, or as a precipitate on the bottom, a scum or deposit in which resided an occult force. It multiplied when introduced into a sweetened must and caused it to ferment: apparently when it was not introduced it formed there spontaneously, and Thénard had shown, in 1803, that all sugared juices which ferment of their own accord, give a precipitate having the external appearance and the properties of the yeast of beer.

This yeast seemed, therefore, necessary to the fermentation. In an experiment which perplexed Pasteur too much for us to pass over it, Gay-Lussac had shown that something else was needed. That able physicist caused to mount to the top of a test tube filled with

mercury, some grapes, the surface of which had been washed many times with hydrogen in order to remove all traces of air from the skins. Then he had crushed them against the top of the tube with the aid of a curved iron rod introduced under the mercury. No fermentation occurred, which might appear very surprising in view of the facility and rapidity with which fermentation ordinarily takes place in the vintage. When it was thoroughly demonstrated that there would not be any, Gay-Lussac brought into contact with the crushed grapes some bubbles of oxygen and saw fermentation begin in a very short time thereafter. From this he concluded that oxygen was necessary to start a fermentation, whatever might be the rôle of the yeast.

The experiment is accurate, although it does not always succeed. Gay-Lussac tried it twice and failed once. That should have been sufficient to make him reflect on the accuracy of his conclusion, but it was decreed that, in this question, suggestion should play a great rôle. Oxygen was then at the height of its glory, and by opening to it the domain of the fermentations Gay-Lussac not only acted in accordance with the prevailing belief, but explained at the same time the preserving methods of Appert, who, in heating his bottles and flasks, was seen to be driving out the oxygen, and, in reality, did not leave any of it behind, as experiment showed. Gay-Lussac explained also the very ancient practice of interrupting fermentation by sulphuring casks or the juice of the grapes. Consequently his interpretation has entered into people's minds, has remained, and has exercised even on the science of our own time an unquestionable influence.

Hitherto, the question had been confined to the domain of chemistry. Since Fabroni (1799), the yeast, whatever its rôle, was considered as a gluten, and it did not occur

to the mind of Thénard to consider it as anything but a chemical compound. As for the intervention of the oxygen, that also was only chemistry. But at this time there appeared in science a new idea, founded on an old observation, made for the first time in 1680 by Leuwenhoeck, then by Desmazières in 1825, and renewed in

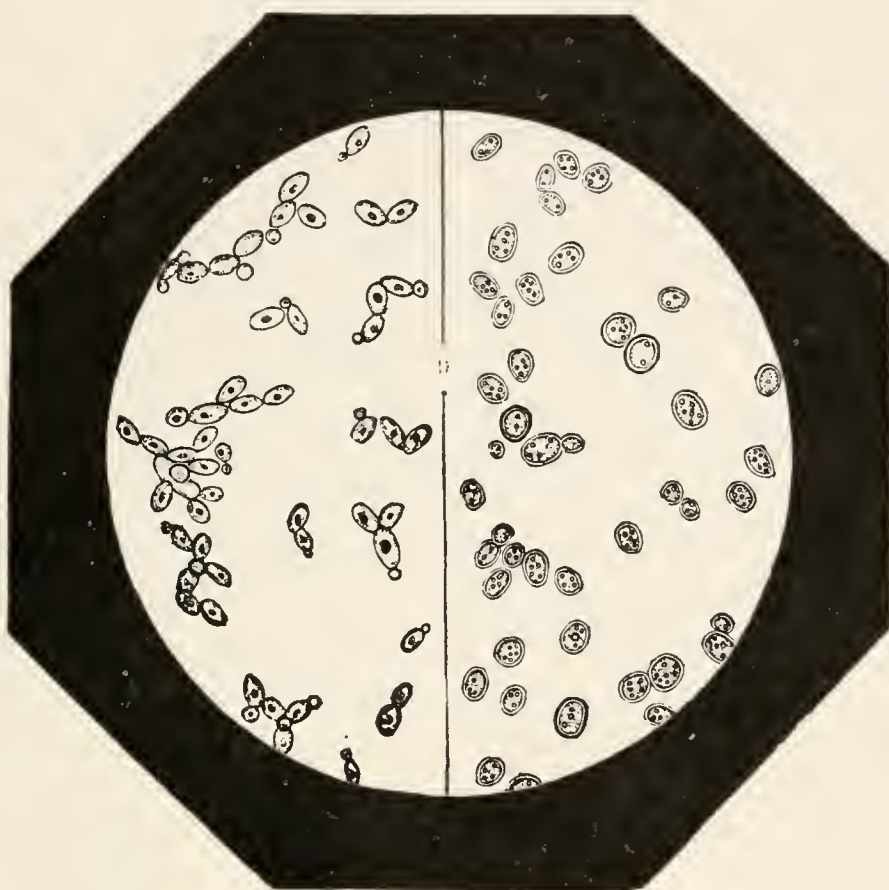


FIG. 7.—Top yeast of beer.

Young.

Old.

1835, almost simultaneously, in Germany by Kutzing and Schwann, and in France by Cagniard-Latour. Subjecting the yeast to a microscopical examination, all these observers had seen that it consisted of ovoid or spherical globules of an organized aspect (Fig. 7), which Cagniard-Latour had the merit to consider as clearly living beings, "Capable of reproducing themselves by

budding, and probably acting on sugar only as a result of their growth."

It was only a phrase. Schwann had brought arguments and made experiments. He had shown in the first place that, contrary to what Gay-Lussac had said, oxygen was not sufficient to start a fermentation. When heated air was admitted to sugared must, the sugar remained intact, and no yeast was produced. But the oxygen in the air had not been touched. That which was lacking was *a something* contained in the air, which the heat had destroyed. Schwann says clearly that this something is a germ; he even says it is a vegetable germ, basing this statement upon the fact that he has found the yeast sensitive to arsenic, like many vegetables, and not to nux vomica, which is deadly to many animals. He found the yeast in the precipitate of fermented beverages; he assured himself that the fermentation begins only when the yeast is present, and is arrested when the yeast ceases to multiply. He recognized the existence of a very close relation between the reproduction of the yeast and the fermentation, and in closing, he expresses the opinion that the plant nourishes itself on the sugar and rejects in the form of alcohol everything that it cannot use.

Almost word for word this is a statement of our present ideas. So perfectly do we agree with it that we ask ourselves why the contemporaries of Schwann were not able to hear his voice. The reason is very simple: they had their prejudices as we surely have ours. They also loved new ideas less than we; they demanded proofs before accepting new ideas, and it is unfortunate that those of Schwann had not the desired clearness. The very short memoir, in which they were set forth, was given out as a preliminary communication, but this was not followed by any more detailed publication.

The experiments, when repeated, were not always successful, especially when, instead of working with sugared musts, organic infusions were used. But how separate, in their causes and origins, phenomena so evidently analogous as fermentation and putrefaction? Opinion remained, therefore, a little hesitating, and the best proof that the old ideas were not disturbed is the work of Helmholtz published in 1843, the first work of the illustrious physicist.

Helmholtz repeated with success the experiment of Schwann, and asked himself what is this *something* in the air which heat kills, or renders inactive. It may be, he said, only a putrid exhalation coming from a mass undergoing fermentation, and capable, by virtue of an unknown power, of provoking a new fermentation: or else it is a living germ. In the latter case, the germ is insoluble in water. The putrid exhalation is, on the contrary, soluble and therefore diffusible. Let us take, therefore, two vessels separated by a membrane; in one let us place a liquid undergoing fermentation, or putrefying, in the other a liquid of the same nature but not fermenting, and let us see what will happen. If the fermentation does not cross the membrane, then it is produced by living creatures; if it does pass the membrane, it must be attributed to something else.

Now the experiment is always successful with liquids undergoing alcoholic fermentation, and rarely or never with macerated meat. That is, the presence of the membrane prevents the alcoholic fermentation from passing, but does not arrest the cause of putrefaction, whatever it may be. From this Helmholtz concludes that there are two kinds of transformation of organic matter, one which takes place with the concurrence of microscopic organisms, and the other without them.

## IV

## LIEBIG

This, then, was the result of the first attempt of the vitalistic theory of fermentation to range itself as an opponent of the purely chemical theory. Cagniard-Latour, Helmholtz, Schwann, were forerunners, but no one listened to them. The uncertainty of their experiments and arguments accounted for this to some extent. There was another and greater obstacle, namely, the general state of the scientific mind of the time. Chemistry had just done such beautiful things, that it believed itself, and every one believed it, capable of doing still more. It did its best to explain everything, down to the most mysterious phenomena of life, by the simple play of physical and chemical forces, and behold how, in a remote corner and one little known to science, it sees reappear in the form of an animate cause, those living forces which it had expelled little by little from the domain of physiology. That seemed to it a step backward. "In what respect," said Liebig, apparently with reason, "does the explanation of fermentation appear to you any clearer when you have introduced into it a living organism, even if it is everywhere in it! But you see for yourself that they are not present in the putrefactions. Let us admit, if you wish, although it seems very extraordinary, that the meat and the sugar are destroyed by different methods. But the sugar can undergo diverse fermentations, very close to the alcoholic fermentation, and even frequently accompanying it: the lactic fermentations, the butyric, etc. Do you find in these fermentations anything resembling the yeast? Do they not behave exactly like the macerations of meat? Your explanation limps, and encoun-

ters obstacles at every step. For me, on the contrary, these transformations present a common character, namely, that of taking place, every one of them, in the presence of an organic substance in the process of decomposition. We start a lactic or butyric fermentation by means of old cheese, or putrid meat. As for the alcoholic fermentation, Colin showed in 1828, that this could be provoked by means of many organic nitrogenous substances, different from the yeast of beer, provided that they are in process of decomposition. It is these dead substances which form the *ferment*. I do not forget the experiments of Thénard on the almost constant production of yeast in juices when in fermentation; I do not forget, furthermore, the conclusions of Cagniard-Latour and Schwann confirmed by Quevenne, Turpin, and Mitscherlich. But this yeast does not embarrass me, it enters into my system. If you admit that it lives, then you admit also that it dies. Now, it is in dying that it acts, as a result of the decomposition which it undergoes at this moment and of that Thénard furnishes us the proof."

That savant had seen, in fact, that by adding 20 parts of yeast to 100 parts of cane-sugar in solution in water, he obtained a rapid and regular fermentation, after which the remaining yeast collected on a filter weighed no more than 13.3 grams. Added to a fresh and equal quantity of sugar, this residue produced a fermentation more slowly than the first time, after which it was reduced to 10 grams, and was incapable of producing a new fermentation. What more fitting to demonstrate that the yeast destroys itself and is consumed by its own activity? The theory of Liebig finds a good defense, therefore, from this point of view. As for the undeniable multiplication of the yeast in the vat of the brewery, in the manufacture of wine, especially of the

white wines, Liebig, who had much imagination, had an explanation all ready. All the fermentable liquids contain what he called *gluten*, what we would call to-day albuminoid substances. In contact with air this gluten oxidized and was precipitated in the form of yeast: this is the explanation of the experiment of Gay-Lussac. Consequently, in proportion as one part of the yeast destroys itself by acting on the fermentable substance, another forms: if more is formed than is destroyed we have the case of the brewery vats; if more is destroyed than is formed, we have the case of Thénard's experiments concerning which we have just spoken.

For the fundamental explanation of the phenomena, Liebig had only to take the ideas of Willis and of Stahl on the internal movement of a mass in fermentation, attributing the motive power to the ferment. "The yeast of beer, and in general all animal and plant substances undergoing putrefaction, impart to other substances the state of decomposition in which they find themselves. The movement which is imparted to their own elements, as the result of the disturbance of the equilibrium, is communicated equally to the elements of the substances which are found in contact with them." For example, sugar is a stable compound with respect to a great number of external influences, air, light, even heat. On the contrary, it is an unstable structure with respect to the molecular movement of organic substances in decomposition: under their action it breaks up easily into alcohol and carbonic acid.

Thus the theory of Liebig, without denying or accepting formally the organization of the yeast globule, confined itself to denying its vital rôle in fermentation, and collected all these phenomena into one single formula. From all sides, it presented a good face,



and as it was defended with energy and talent, it ended by triumphing. Taught in all the books, accepted as true in all the works published on fermentation, it had become almost a dogma, that is to say, what in science is the most difficult to overturn. We may attack facts by showing that they are inexact, experiments by testing their conclusions; but what can we do against a doctrine to some extent philosophic, resting for the most part on argumentation, an argumentation so voluminous that one can demolish certain parts of it without weakening the rest, and which is based on that half mystical conception of an imparted movement?

This detailed exposition was necessary in order to show the state of the question at the time Pasteur approached it, and to understand the nature of the means which he employed to solve it. We shall now be able to go on more quickly: we have reached the level ground.

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V

PASTEUR: LACTIC FERMENTATION

The point which I wish to make clear in the beginning is this: if Pasteur immediately made decided progress in his studies it is because he approached them with another guiding idea than his contemporaries.

In his memoirs, especially in the introduction to his *Mémoire sur la fermentation lactique*,<sup>1</sup> it is easy to find what guided him, but it must be a little more developed. Its origin is an observation made during the study of the rotary power. In many of the industrial fermentations, we meet, as a secondary product, amyl alcohol, a substance endowed with rotary power and capable, further-

<sup>1</sup> Ann. de ch. et de phys., 3<sup>e</sup> série, t. LII. Paris, 1858, p. 404.

more, of forming several crystalline combinations which do not show any hemihedrism. It was the first exception which Pasteur had encountered in this law of correlation between hemihedrism and the rotary power. Now, according to the current ideas of the epoch, fermentation was a disintegration: it was the breaking up of a molecule by decay, the débris of which, still voluminous, formed new molecular edifices which were the products of the fermentation. Consequently, by virtue of the theory of Liebig, the edifice of amyl alcohol must form some part of the framework in the molecule of the sugar in order to resist dismemberment, and as it preserves the rotary power its optical action must be derived from that of sugar.

This idea was repugnant to Pasteur. He had seen, for example, in malic and maleic acids, that the least injury to the structure of the molecule made its rotary power disappear. "Every time," he says, "that we try to follow the rotary power of a body into its derivatives we see it promptly disappear. The primitive molecular group must be preserved intact, as it were, in the derivative, in order that the latter may continue to be active, a result which my researches permit me to predict, since the optical property is entirely dependent on a dissymmetrical arrangement of the elementary atoms. But I find that the molecular group of amyl alcohol is too far away from that of sugar, if derived from it, for it to retain therefrom a dissymmetrical arrangement of its atoms."

The origin of this alcohol must, therefore, be more profound, and, recalling the before-mentioned fact that life alone is capable of creating full-fledged new dissymmetries, and thinking that his objection would no longer have a *raison d'être*, if between the sugar and the amyl alcohol a living organism were interposed, Pasteur

found himself led quite naturally to think of fermentation as a vital act.

Instinctively, for it was still only instinct, he took his stand by the side of Cagniard-Latour and the vitalists. But, in order to defend his position, it was necessary for him to resort to experiment.

In collating the dates of his different publications, it is evident that he began at nearly the same time the study of the lactic fermentation and the alcoholic. Why did he devote his first work to the lactic fermentation, a much less important one from the industrial point of view? Without his telling us, it is easy to divine. In the first place, when the fermentation becomes lactic there is produced, in the greatest abundance, this mysterious amyl alcohol of which we have just spoken. But, from his point of view, there is another deeper reason, that is, that the alcoholic fermentation had already lost its bloom. Liebig and the most determined of his partisans had almost condemned it by admitting that the yeast was necessary, and that it might be a living organism. Their great argument, as we have said above, was always: what rôle would you wish us to attribute to the yeast, when we see so many other related fermentations, the lactic fermentation for example, taking place without it, and without anything which resembles it?

The lactic fermentation was, therefore, in a certain sense, *le champ clos* on which he must struggle, and I believe I am so much the more in the right in attributing to Pasteur this order of ideas because his argument is confined to the following: All that one does with the yeast, I do with the grayish deposit which I find at the bottom of my flasks in which lactic fermentation is going on. The yeast has an organized aspect: my ferment has also, but it is different and difficult to see, and you have not been able to recognize it because, owing to your idea

that the organic matter itself is the ferment, and so much the more the ferment the less it is disorganized, you take for the ferment the altered gluten and the rotted cheese whose amorphous débris covers and obscures the organized ferment. As for me, I have another idea, accord-



FIG. 8.—Ferments of wine and beer: (1) Bacillus of turned wine; (2) lactic ferment; (3) butyric ferment; (4) ferments of ropy wine; (5) ferments of vinegar; (6) amorphous deposit; (7) sarcina. In all of the fields yeast cells.

ing to which the organic matter is only the food for the ferment. I offer this food to it in a liquid state in bouillons or clear macerations, and then my ferment forms, at the bottom of the flasks, a homogeneous layer where it exists alone, or where, when mixed, one can dissolve with

a little acid the carbonate of lime which I have had to add to it. And then it is easy to observe it and to recognize it as an organized being, all the individuals of which resemble one another.

Furthermore, this ferment reproduces itself. Just make, as I did, a clear must containing sugar and chalk: sow there a trace of the deposit from a former fermentation, as small an amount as you wish, and you will see a new fermentation begin. The lactic ferment will multiply, as does the yeast of beer. You will have more of it than you sowed, and with this deposit you will be able to start in different liquids as many lactic fermentations of sugar as you wish, provided these liquids are well chosen, for this ferment, being a living creature, has its special requirements and develops well only when it finds within reach all that it needs.

On the other hand, when this is the case, it accomplishes with rapidity the transformation over which it presides. "The purity of a ferment, its homogeneity, its free unrestrained development by the aid of food substances well adapted to its individual nature, these are some of the essential conditions for good fermentation." Here we have, let us say, in our turn, a revolutionary phrase, one that goes out to meet the enemy, drums beating and fuse lighted.

There is still more in this short memoir of 15 pages. There is a very exact statement of the good or bad influence, as the case may be, of the acidity or alkalinity of the liquid. The yeast prefers sugared media which are acid; the lactic ferment, neutral sugared media, and it is for that reason we add to the cultures carbonate of lime. There is also a hint, as it were an apparition, of the effect of antiseptics. "The essential oil of onion juice inhibits completely the formation of the yeast of beer: it appears equally harmful to Infusoria. It

can arrest the development of these organisms without having any notable influence on the lactic ferment." Thus one could use antiseptics, with a suitable culture medium, for separating the ferments one from another.

This memoir then is full of suggestion, and, strangely enough, all these propositions which were so new and so bold for the epoch were announced *de plano*, almost carelessly, with the tranquil confidence of a man sure of his facts, and to whom, if one did not know him, one might even have attributed malicious intentions, he showed so much apathy. It is only at the end of his memoir that he admits that nothing of all this has been demonstrated. "If any one should say to me that in my conclusions I go beyond the facts, I would reply that that is true in this sense that I have taken my stand unreservedly in an order of ideas which, strictly speaking, cannot be irrefutably demonstrated." But his system is so logical that he takes pleasure in believing in it. Everything is so consistent in his conception and in his mode of exposition. The idea of a specific ferment associated with each fermentation, of disproportion between the weight of the ferment produced and the weight of the matter transformed, of vital competition between two organisms which simultaneously invade the same medium and ultimately leave it to the one which is best adapted to the conditions it finds there, —all these ideas, which the future was to develop so far, are found not in embryo, but clearly set forth in this paper, the work of exuberant youth, in which we still see the thought bubbling and fermenting. Pasteur ended it with a general profession of faith: "It is now my opinion," he said, "as the result of the knowledge I have gained on this subject, that whoever will judge impartially the results of this work and those which I shall publish in the near future, will recognize with me

that fermentation is correlative with life, with the organization of globules, not with the death or putrefaction of these globules, neither does it appear to be a phenomenon of contact where the transformation of the sugar takes place in the presence of the ferment without giving anything to it or taking anything from it. These latter affirmations, one will soon see, are contradicted by experiment.”

This was the announcement of the memoir on alcoholic fermentation, to which we are now come.

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## VI

### ALCOHOLIC FERMENTATION

In the memoir on alcoholic fermentation<sup>1</sup> the movements and the tone differ wholly from those of the memoir which precedes. The latter is not that tranquil and almost ironical exposition of a new theory which holds up its head and marches along easily over a land where its competitors hobble and stumble, or where they have need at every step of what Victor Hugo would have called crutch hypotheses. It is a series of blows straight from the shoulder, delivered with agility and assurance.

Ah! You insist on thinking of alcoholic fermentation as a simple breaking up of sugar into alcohol and carbonic acid! Undeceive yourselves: there are also glycerin and succinic acid formed in considerable quantities and almost as constantly as the principal products of the fermentation.

Ah! So you are bound to ignore the yeast in this phenomenon, or at the most will concede to it only the rôle of an initiator! Very well! Learn that this yeast

<sup>1</sup> Ann. de ch. et de phys., 3<sup>e</sup> série, t. LVIII, 1860.

always borrows something from the sugar, and makes a part of its own tissues out of this food. Learn also that it is only on the condition of keeping a little of the sugar for itself, that it consents to give you the rest in the form of alcohol.

Ah! Do you believe that you can write an equation for the alcoholic fermentation as you write the equation for the preparation of oxygen? Very well! Simply to account for the production of the glycerin and the succinic acid, the equation must be very complicated, and if you wish to take into consideration the things borrowed by the yeast from the sugar, it will become so complex that it would be better not to write it at all. Would you dream of writing in the form of an equation the series of transformations which are undergone by the sugar in the tea or coffee you drink? The yeast is a living thing just as you are.

This is a résumé of the attack directed by Pasteur against the old ideas, and when he had demolished them, he set about their reconstruction. Omitting some of the less important details, and taking up the exposition proper, the edifice, it must be admitted, is simple: it amounted to this, to produce regular fermentation under conditions in which none of the prevailing theories could explain the phenomenon.

It is curious to see how the idea of this pertinent experiment came to Pasteur little by little.

Thénard, we have seen, had determined that there was a diminution in the weight of the yeast during fermentation, which is true for the conditions of his experiment. He had found, furthermore, that this yeast, when exhausted in the presence of an excess of sugar, no longer contained nitrogen. This last was an error, due to the imperfection of the methods in use for the detection of this substance.



On this first error, Döbereiner grafted another by affirming that the nitrogen lost by the yeast was found in the fermented liquid in the state of ammonia. As organic matters in decomposition also produce ammonia, this affirmation of Döbereiner was, clearly, very favorable to the ideas of Liebig, and the latter, a great collector of fact and abstracter of quintessence, did not fail to seize on this and make it serve to prop his doctrine of fermentation.

For Pasteur, on the contrary, this fact was inexplicable, since the ferment was not a dead substance in process of destruction, but a living thing in process of organization. In trying to discover whether the statement of Döbereiner was true he found not only that the nitrogen of the yeast did not leave it in the form of ammonia, but, moreover, that the yeast in process of fermentation caused the ammonia to disappear from ammoniacal salts added to the liquid.

But how could the yeast do this? He then was very bold to reverse the reasoning of Liebig and of Döbereiner, and to say: the albuminoid substance of the ferment does not give up ammonia; it is, on the contrary, the ammonia which produces the albuminoid substance.

This way of looking at it was so new and the presumption seemed so ill-founded that Pasteur hesitated, as he himself acknowledges. But it was in accordance with facts and the logic of his ideas. In any case, the only thing to do was to resort to experiment. After some attempts, the latter succeeded, and it became the critical experiment, the *experimentum crucis*, which made it possible to judge the doctrines side by side.

This experiment was entirely new. The problem was to grow the yeast in a liquid deprived of all organic nitrogenous matter—one containing only perfectly pure cane-sugar, various mineral salts to supply the yeast

globules with the elements of their structure, and an ammonia salt to provide them with nitrogen. If, in this medium, completely robbed of that organic nitrogenous matter which Liebig declared to be necessary, one obtains a fermentation, and if, at the same time, the yeast multiplies and develops, deriving all the complex elements for its tissues from the sugar and the ammonia, it will certainly be impossible not to admit a correlation between the fermentation and a phenomenon of development and of life in this ferment which Liebig considered a dead substance.

With the same blow by which the theory of Pasteur triumphed there fell into ruin not only the theory of Liebig, but another theory then much less flourishing, namely that of Berzélius, according to which the ferment exerted an action only by its presence, and provoked the decomposition of the organic matter without deriving anything from it or contributing anything to it, remaining, furthermore, unchanged in quantity and quality throughout the process. In our experiment, the ferment must, on the contrary, increase in weight, taking all this increase from the sugar.

It is just because this experiment was so interesting that it was difficult. It was necessary, in the first place, for Pasteur to devote his attention to supplying the yeast with a suitable mineral medium, and a rather complex one too, including phosphates, salts of potassium, magnesium, and ammonia. It matters not that the cell of the yeast is small; its needs are great and varied. It was the first time that Pasteur had run up against its exacting requirements, and the lesson which he drew from this contact was not lost. Furthermore, even when one gives to the yeast all that it needs in the way of mineral substances, it has much more difficulty in living in this medium where it must form all the substances

constituting its tissues, than in the juice of the grape or the must of beer where it finds everything composed of utilizable elements. Nevertheless, in his *Mémoire sur la fermentation alcoölique* Pasteur succeeded in giving an example of fermentation accomplished under these difficult conditions.

Later, feeling the importance of this experiment, he returns to it, perfects it, and renders it surer by employing a more vigorous yeast than that of his first experiments. It is scarcely 13 years later in his *Études sur la bière* that he gives it the definitive form. But what he says in his memoir of 1860 is sufficient to carry conviction.

No, it is not true, he said in substance, that there is need of organic material in decomposition in order to start alcoholic fermentation. An imperceptible trace of yeast, introduced into a liquid containing, in addition to the pure sugar, only pure crystallized mineral salts, makes this sugar ferment and, at the same time, the yeast develops, buds and multiplies. All the carbon of the new globules is derived from the sugar, all their nitrogen from the ammonia, which destroys also the theory of Berzélius, according to which the ferment acts only by its presence, in the same way that a red-hot cannon-ball would start a fire. Moreover, it is not simply in the absence of already manufactured organic nitrogenous matter that the yeast globules borrow from the sugar what they need: on the contrary, there is every indication that this borrowing follows exactly the same laws when the liquid is more favorable to fermentation.

There is, nevertheless, a difference, namely that in those rich liquids, the musts, the new globules which form, finding themselves surrounded by nutrient substances, have no need of borrowing anything from the globules already formed, while in an exhausted medium

such as sugared water, the new globules live at the expense of substances which the older globules have allowed to diffuse into the liquid. All are famished and then the young consume the old. It is this work of diffusion and of exhaustion of globules already formed in order to feed the young, which caused the diminishing weight of the yeasts sown by Thénard in the sugared water in the experiments cited above, and which has led to the belief that the yeast is destroyed in fermenting the sugar. In reality, there were not enough of the new globules formed to compensate for the loss of weight which the old globules underwent as the result of the diffusion but if we add to the weight of the globules the weight of the soluble organic matter which the filter does not retain, but which we can find and estimate in the liquid, we see that this total weight always increases during the fermentation, because there is always a little sugar which becomes yeast.

In proportion as the fermentation is accomplished under better conditions and the yeast is less exhausted toward the end, the increase in weight is more notable. We are aware of this from the fact that the yeast continues to give off carbonic acid at the expense of its own tissues for some time after all the sugar has disappeared from the liquid which bathes it. We would say to-day that it consumes the reserve food which it has made, for it is a provident little cell which stores up in a time of plenty for a time of famine. How is it possible not to see that all this is a question not of decomposition and of death, but, on the contrary, of development and of life?

## VII

## AËROBIC LIFE AND ANAËROBIC LIFE

And Pasteur, in all the enthusiasm of his discovery, adds or did add soon: It is not simply for alcoholic fermentation that this is true. I can return now to affirmations respecting the lactic fermentation, which it is very easy to start in a purely mineral medium. The lactic ferment is smaller and in appearance simpler than the alcoholic ferment. It is a little cell constricted in the middle (2, Fig. 8) and the whole interior of which is filled with a mass that appears to be homogeneous, whereas it is differentiated in the yeasts. But the needs of this little cell are not less: they are different, that is all. These two dissimilar ferments are, moreover, specific, that is to say the alcoholic ferment does not produce lactic acid, contrary to what is generally believed and taught, and the lactic ferment does not yield alcohol when it is alone and unmixed with the alcoholic ferment.

Do not believe, furthermore, with Boutron and Frémy, that successive fermentations can take place in the same medium with or without order, according to the mode and progress of the decomposition of the nitrogenous substance. That happens when your spoiled meat or rotted cheese carries with it into the fermentation flask the numerous organisms which ordinarily populate it: it does not happen when you grow a pure ferment in clear nutrient bouillons. You are told that the butyric fermentation, the mannitic, etc., accompany or follow lactic fermentation. It is not so, everything stops in my flasks when all the sugar is transformed into lactic acid, now become lactate of lime by contact with carbonate of lime introduced into the liquid.

But, while keeping them separate, we can make these fermentations follow each other, although, according to the ideas of Liebig, they are interblended. Take this liquid in which the lactic ferment has grown, and in which there are only lactate of lime and mineral salts in solution: after having heated it to sterilize it, sow there a drop of a liquid in which there has occurred spontaneously a butyric fermentation, and, therefore, one which is almost surely impure. Phenomena analogous to those of alcoholic fermentation occur: a gas is liberated which is no longer a pure carbonic acid, but a mixture of this gas and hydrogen. This mixture has very little odor, because of the absence of sulphuretted hydrogen. These are the indications of a fermentation. Let us see now what is present in the liquid which has become clouded. We find there only motile rods, very agile, with undulating movements, sometimes ranged in a series, like a string of boats, and then motile on their articulations (Fig. 8, sec. 3), which testifies to the fact that they reproduce and multiply by elongating and segmenting across their longer axis; this is the mode of reproduction called *fission*.

When he observed for the first time those organisms which he called vibrios, Pasteur had a great surprise, the trace of which is visible in his note on this subject. The yeast of beer and the lactic ferment were non-motile globules; the butyric ferment was motile, and partook of the nature [animal] of those organisms which Ehrenburg and Dujardin had found in infusions. O the power of words! Nothing was more natural than to find in fermentations the same organisms as in infusions, since Pasteur nourished his ferments with vegetable infusions; he hesitates, however, on finding that the butyric ferment belongs to the Infusoria. "I was so far," he said, "from expecting such a result, so far, indeed, that for a long

time I thought it my duty to apply all my efforts to dispelling the apparition of these little animals, from the fear lest they nourished themselves on the vegetable ferment which I supposed to be the butyric ferment, and which I was trying to discover in the liquid medium that I employed. But not able to find the origin of the butyric acid, I ended by being struck with the coincidence which my analyses showed me to exist between this acid and the Infusoria, and, reciprocally, between these Infusoria and the production of this acid. We must consider them the true butyric ferment."

Thus Pasteur's surprise came from the intervention in a fermentation of an organism which he considered to be an animal because it was motile, while the non-motile alcoholic and lactic ferments were considered as vegetables. We can to-day scarcely understand this astonishment and these scruples. But from 1850 to 1860, the old barriers established between the vegetable and animal world had scarcely begun to fall. Although admitting in his *Recherches sur les zoospores des algues*, which appeared in 1851, that the green Infusoria and the Volvocaceæ "present animal characters too pronounced and too permanent for it to be possible to relegate them to the vegetable kingdom," de Thuret insists, none the less, on the difficulty of tracing an exact line of demarcation between animals and the lower vegetables. "At this time," writes my excellent confrère, M. Bornet, "motility appeared to be so evidently an animal character that Rabenhorst published, between 1849 and 1852, a collection of Diatoms and Desmids as *Ein Beitrag zur Fauna von Deutschland*." Pasteur, who was not a naturalist, was excusable for still holding this opinion in 1862, and although astonished at his scruples, one must be pleased with him for taking so much pains to efface them from his mind. He did not suspect then that this discovery

would open a new world, the world of the bacteria, a world still more active and more densely populated than the world of the yeasts.

There was, in this same Note which we are analysing, a fact much more important than the animal or plant character of the butyric vibrio: namely, that this organism lives in the absence of the oxygen of the air and even fears its contact. Pasteur has often related how this fact leaped, so to speak, into his field of vision. In examining these liquids, he would take a drop, place it on the slide, cover it quickly with a cover glass, which spread it out in a flat layer, and put the preparation under his microscope. But on examining, with the care which he applied to everything, one of these little flattened drops of liquid undergoing butyric fermentation, he was astonished to see that on the margins of the little drop, wherever it was in contact with the air, the bacteria had become non-motile and inert, although they continued to move with agility in the central portions. This was a spectacle quite the reverse of that which he had had occasion to observe often in the case of the animalcules of the infusions. Especially when we examine, under the microscope, those from the surface of infusions, they voluntarily leave the central portions of the drop to approach the margin, the only place where there is enough oxygen for all. In the presence of this observation, Pasteur asked himself immediately: is it true that these vibrios are trying to escape from the oxygen? An experiment along this line was easy to make. By passing a current of air through a flask in which the butyric fermentation was going on, the fermentation was retarded or arrested, and behold a new idea was introduced into science, the idea of anaërobic life as opposed to aërobic life which was believed to be that of all the animals of creation. We shall see how Pasteur



developed this idea later. For the moment we may content ourselves with saluting its dawn.

This idea has, nevertheless, an indispensable complement which we can and must give immediately. There is oxygen everywhere, in the air and in the water. It is in the liquid in which we have sown our bacillus which is unable to bear the air, our anaërobic vibrio. How is it that it can develop in this aërated medium? It is because we have, unawares, sown with it in the liquid some aërobic organisms which have consumed its oxygen, and, this being achieved, have fallen inert to the bottom, permitting the butyric vibrio to take possession of the medium. If the liquid is in contact with the air some of these aërobic organisms have remained on its surface. There they continue to live, to swarm, and they form a gelatinous layer which is, for the oxygen, a barrier as impermeable as a wall of glass; all of it that is able to penetrate is absorbed in the passage, and, thanks to this aërobic life on the surface, the anaërobic life can pursue its course in the depths without hindrance.

Having come to this simple and satisfactory conception, it was not the moment for him to stop. Up to this time we have observed only the phenomena of the fermentation of sugar, or of the lactate of lime. Let us now turn our attention to an albuminoid substance, beef bouillon, egg albumen, meat macerated in water. Let us, as we have done hitherto, begin the operation by introducing into it a drop of an organic liquid undergoing putrefaction: we shall see the same phenomena begin again. There is formed once more on the surface of our liquid a living layer which will absorb the oxygen and will leave the interior of the mass free for the anaërobic life. If our liquid is contained in a closed flask, one or several aërobic generations will dispel the oxygen, and will leave the field free to the anaërobes. There

will be produced once more the gases, which this time will have an odor, because in this reducing medium, hydrogen is mixed with sulphuretted and phosphoretted hydrogen, which are not formed in contact with air, or, if formed, are oxidized immediately: we shall have, therefore, a putrid odor. But the gases will have the same origin as in the fermentation of lactate of lime. Fermentation and putrefaction are synonymous terms, and there is no reason for maintaining the old distinction, which had not yet disappeared from the conclusions of Helmholtz. In these two phenomena the liberation of gases has the same origin, and it is due to organisms living in the absence of air. It is opportune to ask if there is not a close relation between the phenomena of fermentation and of anaërobic life. Here we have a great question which Pasteur put to himself immediately, but which he did not solve until some years after.

I have thought best to present without detailed examination all these deductions, because in reality they were the work of some weeks of labor and meditation, and also because we have in them an example of Pasteur's insight, of his ability to discover and state a problem, of the patience with which he gathered together the elements of the solution. During the best years of his life, this man lived in advance of his time, a pioneer lost in the solitude, absorbed in the contemplation of the vistas which he was discovering, and which his eye alone was to scrutinize and survey. What less astonishing than his apparent indifference to things of daily life! He lived in his thoughts without being a dreamer, for a dream which goes somewhere and which bears fruit is no longer a dream.

## THIRD PART

### SPONTANEOUS GENERATIONS

#### I

#### SPONTANEOUS GENERATION AND FERMENTATION

Pasteur's contributions to the study of fermentations, which we have just seen going on under our eyes, may be summed up in a few words. Fermentation is no longer a vague transformation, indeterminate in its cause and in its origins, capable of taking place under the influence of any organic substance whatsoever: it is a specific phenomenon, due also to the existence and development of a specific organism, the study of which under the microscope is facilitated in proportion as we remove from the liquid undergoing fermentation those insoluble organic substances which it was formerly believed necessary to add to it. Since, by working with a clear bouillon, it is possible to follow closely the organism sown, and to be sure that the bouillon contains this and this alone, the study of its nutrition becomes easy. Now, by acting on the nutrition of an organism, we become the master of it; we can sow it and cultivate it with as much certainty, and with the same absence of weeds, as we can lettuce in a garden. We can also banish it from liquids where there is no occasion for its presence. In short, this infinitely small organism becomes tangible and open to experiment: a capital idea, which the whole life of Pasteur will henceforth be spent in developing.

Nevertheless, the logic of his studies placed before him

a question which, with just reciprocity, these same studies permitted him to solve. Whence come the ferments? Are they organized spontaneously at the expense of dead organic matter? Or, do they come in the regular ways from organisms like themselves, and from pre-existing germs? Here we have a question which had been asked very often, ever since men had begun to reflect, and which had been solved in very different ways. Pasteur, himself, at the close of his studies on crystallography, had been very undecided, and I think also very indifferent regarding the answer. He had no preconceived ideas: he would accept the results of experimentation. But at the point to which the study of fermentations had led him, he could no longer believe in spontaneous generation: it is too far removed from the idea of specificity, which he had just introduced into science. Everywhere around us the idea of species accompanies the idea of continuance by the germ cell, and it would be very astonishing if this order were changed in the world of the infinitely little.

The ancients believed in the spontaneous generation of eels from the ooze of rivers, and in that of bees in the entrails of a dead bull. But these were the ideas of a child who had never lived in the face of the progress of knowledge. For a long time people had believed in the spontaneous generation of worms in putrefying meat, because in this case the experiment is more difficult or the observation is more delicate, and a Redi was necessary to demonstrate that these worms come from eggs laid by flies, and that one would no longer see them in a piece of meat which was protected by a simple layer of gauze. It is true that this piece of meat continued to putrefy, to decay, and to nourish, no longer worms but confused tribes of microscopic organisms. As long as it was the belief that fermentation and putrefaction oc-

curred by chance, without any order or regulation, it had been possible to believe that the organisms which accompanied them were also due to the spontaneous organization of the elements of the meat undergoing putrefaction, or of the organic matter added to the liquids of fermentation. But as soon as these fermentations and the organisms which produced them assumed something of a specific nature, there was something strange in making them come into existence spontaneously. Why should chance create species endowed with hereditary properties? Why should it create certain organisms and not others?

The knowledge of fermentations which Pasteur had just acquired forced him, therefore, to deny the hypothesis of spontaneous generations. He observed, furthermore, that after having abandoned all pretense of explaining the origin of animals visible to the naked eye, and thus accessible to experiment, this hypothesis had limited its domain to the realm of microscopic organisms whose minuteness precluded all exact scientific research. But in this quarter he had had some experience and could hope to escape some of the difficulties which his predecessors had encountered. In spite of the advice of M. Dumas, he, therefore, approached this subject with confidence.

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## II

BUFFON, NEEDHAM, SPALLANZANI, SCHULTZE,  
SCHWANN, SCHROEDER AND DUSCH

Like the question of fermentations, the question of spontaneous generations had for long years been the subject of philosophical speculations and oratorical dissertations. Buffon had treated it with solemnity. How remain indifferent in the presence of the very

sources of life, before this phenomenon which endows with a new existence the organic atoms which death has just dissociated and liberated? There is no death, said the believers in this doctrine. When an animal dies, the life of the whole vanishes but not the life of the elements, not that of its ultimate molecules. Scarcely are they set at liberty by death, than they at once begin an independent life, become isolated, and then give birth to vibrios, to monads, or else they join already formed aggregations which attract them, and thus produce the large Infusoria. "Therefore," said Buffon, "it is inevitable that one should encounter all imaginable gradations in this chain of organisms which descends from the most completely organized animal to the simple organic molecule."

We see the connection between these ideas and those which during the same epoch explained the mystery of fermentations. It was the same organic molecules, dissociated by putrefaction, which provoked the decomposition of fermentable substances by communicating to them their own movement, and which, on the other hand, became organized into living animalculæ. Singularly, this idea of a common origin did not prevent the fermentation of a liquor from being considered as something quite independent of the Infusoria which might appear therein, and these two kinds of evolution of the organic molecule were even regarded as opposed to each other, and the Infusoria as harmful to the fermentation which was called the principal phenomenon.

What a strange way of looking at things! we might say to-day. Why turn the carpet over in order to see the design? When we know a little of the history of science, we are no longer astonished at this kind of blindness. Our conceptions of things are generally more complicated than the things themselves. It is rare that the

human mind *sees simply*: it is experiment alone which leads it to simplification by ways which are sometimes very tortuous. But to attain that end it is necessary that the mind allow itself to be guided, and that it forget its conceptions and its formulas. Nature is kindly; it is we who picture her as bristling and sulky!

In the domain of spontaneous generations, experiment had been introduced for the first time in 1748 by an Irish Catholic priest, Needham, whose active faith did not prevent him from believing in an actual creation, that of the animalculæ of infusions. In order to prove this, he had employed a mode of investigation destined to play a great rôle in the controversies on the question. He had enclosed some putrefiable substances in well-corked flasks which he had then heated by plunging them into hot ashes. The heat, he said, must kill all the living germs, visible and invisible, which may be introduced into the flasks, for none are known which resist boiling water. Now, as my closed flasks withdrawn from the ashes become clouded in a few days, and are peopled with microscopic organisms, I am assisting at a phenomenon of creation at the expense of dead matter, that is at a spontaneous generation.

These experiments, accepted for a long time without question, met in 1765 a redoubtable critic in another abbé, the illustrious Spallanzani, who, by repeating the same experiments, with only the precaution of heating the closed flasks longer than Needham had done, suppressed all production of Infusoria. Therefore, he concluded, Needham did not heat enough, and as it was for him to prove his theory, which, besides, is in disagreement with the facts of science, it vanished of its own accord, the only fact on which it could rest having been shown to be inexact.

Not at all, replied Needham, although with much

courtesy. If your infusions remain sterile it is because you heat too much. You alter thus the air in the flasks, or else you destroy the *vegetative force* of your liquids. The first of these objections was acceptable, although it lacked force and precision in an epoch when the composition of the air was still unknown. But what was to be said of the second? The vegetative force of the liquid, does not that recall invincibly the dormative property of opium, ridiculed a hundred years before by Molière? This strange conception, nevertheless, met with favor, and, if I recall it, it is because the idea served as a banner. If, in the discussions on spontaneous generations, there have always been savants, who, like Spallanzani, have endeavored never to go beyond experiment, there also have been always those who, like Needham, have not hesitated, in a time of great need, to have recourse to the *vegetative force*, to the *creative power* of infusions, or to other conceptions not less vague and chimerical. There, as everywhere, has been the tribe of those who love to deceive themselves with words.

Be that as it may, the celebrated debate raised between Needham and Spallanzani was left without any definite conclusion, each of the adversaries showing clearly that the other was wrong on some points, but not proving that he himself was right on all. However, science in its onward march validated or invalidated their arguments. We have said that Gay-Lussac, by studying the conserves of Appert, which were nothing more than the application to domestic economy of the results of Spallanzani, found that the air in the tins no longer contained oxygen: this seemed to justify the first objection of Needham given above. But in 1836, it occurred to Schultze to replace with ordinary air the air in the flasks of Spallanzani. After having determined that they are sterile, he shows that they remain sterile



when he introduces air which he has simply made to bubble through concentrated sulphuric acid. One of these experiments lasted from May to August, but, although this air was incessantly renewed, it never caused any production of Infusoria: this proved that Gay-Lussac was wrong, and Spallanzani right.

The following year Schwann obtained the same result as Schultze by using air heated by passage through a bath of fusible alloy. Later (1854), Schroeder and Dusch replaced the heated air by air simply filtered through cotton, and from them dates the introduction into microbiology of cotton plugs for filtering air.

Reading to-day of their experiments, we ask ourselves why they did not bring universal conviction. What did they signify save this: that there was in the air a principle of life which sulphuric acid, heat filtration, through cotton, destroyed? This principle was, therefore, neither a gas nor a vapor, nor one of those solid bodies which heat respects. It could only be an organic substance. How is it that Schwann and Schultze did not as resolutely bring the partisans of spontaneous generation face to face with this dilemma, as Pasteur was to do 10 years later: this organic substance which heat and sulphuric acid destroy, which cotton arrests, can only be living or dead. Why, being forced to choose, do you take the hypothesis the most contradictory to that offered by the best known branches of science?

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### III

#### POUCHET, PASTEUR: THE GERMS OF THE AIR

In order to assume this tone of authority, it would have been necessary to confront the partisans of spontaneous generation with some experiments which were

irreproachable and always successful, but no such were available. Experiments which had been the most convincing often failed, without any one being able to tell why. Even to-day, when our technic is better, we can not be sure of obtaining the results of Spallanzani. Tyndall, whose experimental skill was very great, has often repeated in vain the experiments of Schultze. In short, there were certain substances, milk, albumen, macerations of meat, which neither filtration, nor heating of the air preserved from alteration, and we have seen that Helmholtz admitted for these substances a kind of spontaneous generation. But to admit it in one case, was to admit it in all. Wherever there was a doubtful case, one flask remaining fertile in spite of the precautions taken, spontaneous generation had the right to seize upon this result, and to say "It is I who have produced this. Life is a fragile thing to preserve; more fragile still to produce. It is all to no purpose that you train your fingers to manipulate it delicately; you thwart it without knowing it, and it is sometimes just because you are unskilful that you see it appear."

And these were not the only reasons. The partisans of spontaneous generation had the best of it in the discussion, and they could say: "We who do not know on what life depends and who make it arise from nothing, we are exempt from the obligation of showing you its origin and causes. But you who attribute it to pre-existing germs, show us then these germs! Above all, show them to us in sufficient number and variety so that each bubble of air can people with numerous and varied organisms the various infusions which we may ask it to fecundate. For, finally, specificity is one of the consequences of your way of looking at things. But we have not forgotten a certain experiment of Gay-Lussac in which some grape juice, sterile at first, was made to

ferment upon the entrance of some bubbles of air. You say these bubbles brought with them some germs of yeast, but they brought something else into an infusion of hay, and still other germs into a meat infusion, etc. That makes a great many germs!" And Pouchet, who was a man of imagination, added: "The air thus peopled would have the density of iron."

To all these reasons for doubt, add this one, to which we have referred above, and which was more profound and more powerful, being more general, namely that, in the phenomena of spontaneous generation, even more than in fermentations, chance seemed to be master and to dictate according to its caprice the kinds of population of the infusions, and of destruction of their elements. Spontaneous fermentations, spontaneous generations, chance, all these words harmonized well and entered *en bloc* the minds of the scientific men.

It is here that we again recur to Pasteur, and to that quality of which I have just spoken—the superiority of his equipment for entering the fray. The idea of specificity, born of his work on the fermentations, involved that of hereditary characters, which in its turn led to that of an ordinary kind of generation. Pasteur inclined, therefore, logically toward the theory of germs. It was only a question of proving it by experimentation, and for that he was better equipped than any scientific man of his time. He was familiar with the infinitely small organisms; he knew how to manipulate them. He had a clear field: and he advanced with great strides.

"You pretend," he said to the partisans of spontaneous generation, "that there are not enough living germs in the air to explain the fertility of the infusions with which this air comes in contact: what do you know about it? You have examined the dust deposited on furniture and on stones; you have gone to investigate it in the aban-

doned towers of old cathedrals, and at the bottom of the hypogea in ancient Egypt. Futile pains! It is not the dust which falls and is deposited that interests us! You will find therein only the heaviest parts of what the wind carries, mineral particles, grains of starch or of pollen, the spores of cryptogams or even bits of down, of cotton, of wool from the living sheep or from our garments. It is not these particles which we must study, but rather those which we see dancing without repose in a ray of sunlight, and which the air contains in the state of a permanent suspension."

"Furthermore, your study of the dust of cathedrals gives you no indication of quantity. What is the volume



FIG. 9.—Dust of the air caught by aspiration in the meshes of gun-cotton.

of air which has deposited the little mass which you have studied, and subjected to microscopic examination? You do not know, and consequently your experiments may well open the question, but they do nothing to solve it."

"Nevertheless how easy the thing is! Let us take the cotton filter of Schroeder and Dusch, and replace it only by gun-cotton, and when by it we have arrested in its passage the dust in a determined volume of air, let us throw the gun-cotton into a mixture of alcohol and ether in which it is soluble. All the weft of the filter is dissolved. The particles of dust which have been caught in the meshes are set at liberty and fall to the

bottom of the liquid if one leaves it in repose. We may then decant the liquid above them, wash them, reunite them finally in a little volume of water and study them. And behold what we have! Look and tell me if there are not there present corpuscles, spherical globules (Fig. 9), round or oval bodies, so like the spores of cryptogams or the eggs of Infusoria that no micrograph could distinguish them. As for their number, we find many thousands in a little plug of cotton through which has been passed for twenty-four hours a moderate current of air, and as we count only the largest of these globules figured here, those which have a clearly organized aspect, while we leave aside the smallest, which are evidently the most numerous, failing to distinguish them from amorphous elements, you must conclude that there is constantly present in the air in a floating state the means of life for all the infusions which you put in contact with it."

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#### IV

#### IN THE AIR THERE ARE LIVING GERMS

"But," you will say, "what assurance have you that these particles of dust which you have shown us are living, or at least that they contain something living? That is also easy to prove. We take the flasks of Spallanzani, or of Schwann, for, mark it, I do not introduce any new method of work, I am content with operating well where others operated badly, with avoiding causes of error which rendered the experiments of my predecessors uncertain and contradictory. We take then a flask containing a vegetable or animal infusion: draw out the neck of it in a flame, then boil the liquid in order to destroy by heat everything living that it

contains (Fig. 10). We remove the air which it contains by the current of vapor which the boiling produces: we shall sterilize at the same time all the interior walls. On leaving the neck of the flask, the vapor traverses a platinum tube heated to redness in a gas furnace (F, Fig. 10), and then escapes into the air. When the boiling has lasted some minutes, we extinguish the flame under the flask; the liquid cools; the vapor condenses: it is replaced by air which will have traversed the red-hot tube of platinum, where everything organic contained in it will have been burned. When the flask is cold, we separate it from the rest of the apparatus by fusing

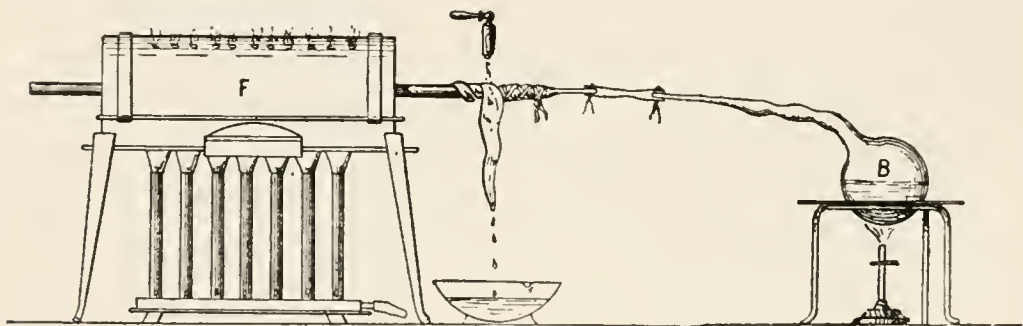


FIG. 10.—Method of heating the air (to free it from germs) before introducing it into flasks.

its tapering neck in a blowpipe. We shall have there a flask of Spallanzani, that is to say an organic infusion in contact with air containing all its oxygen, but robbed of everything living, and even organic, which it contained. Very well, nothing will be produced there; the infusion remains clear because we have allowed nothing living to enter it.

“Now, for this is not the end, we take one of these flasks which has remained sterile, and by a simple process, which I shall not stop to describe, we pass into its neck, always in the presence of air sterilized by heat, one of these little pieces of cotton soiled by the dust of the air, the living character of which you deny. As long as

this remains in the neck (Fig. 11), the liquid of the flask retains its first clarity. At the end of 15 days, or a month, we make the cotton fall into the infusion by simply inclining the flask, and we shall see that at the end of 24 hours, the liquid will become clouded, and that after 48 hours it will contain millions of living organisms. When birth is given there to cryptogamic growths, we shall often see tufts of filaments growing out around the cotton of the plug, testifying thus to their affiliation with the germs which it contained.

“What reply will you make to this experiment? The microscope has shown us in the bit of cotton substances of an amorphous aspect and substances with an organized aspect. This we can affirm as a result of our first experiment. The second, which I have just described, tells us that among the substances on the cotton there are some that are living. You partisans of spontaneous generation, you are condemned to seek by preference in amorphous and dead substances the enigma of the life which appears in the infusions. Behold the inconsequence into which my experiments drive you, for, mark it, they are no longer doubtful, irregular, contingent experiments, but they succeed 100 times in a 100, provided a little skill is used in performing them. They are obedient to the mind as though following to the letter the excellent program drawn up by the Academy of Sciences: ‘They are freed from all uncertainty arising from the experiments themselves.’ Repeat them with the details which I give you and you will succeed just as I have done.”

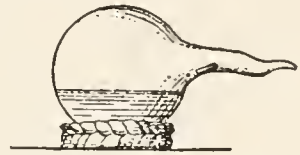


FIG. 11.—Flask used by Pasteur in his study of fermentations and of the distribution of germs in the atmosphere.

One can divine the effect of an argument so concise, and having the charm of a geometrical demonstration.

Pasteur did not stop midway. "Do you pretend," he continued, addressing the partisans of spontaneous generation, "that the cotton, as such, plays some part in the phenomenon? Never mind! We will replace it with calcined amianthus, without in any way changing the result. You pretend that the cotton would have absorbed, by contact with the air which has traversed it, some vapor, or I know not what subtile matter which heat can destroy, and which, entering the infusion with the cotton, would have brought there one of the conditions necessary for life. Your hypothesis is somewhat intangible. But there is nothing more mysterious than life itself, and I will reply to it.

"After having introduced into the flask an infusion capable of fermentation, draw out the neck in an enameller's lamp, in such a way as to make a bent and sinuous tube, in the form of a letter S (Fig. 12). Then boil the liquid. When vapor has issued from the orifice of the neck for some minutes, drawing out all the air of the flask with it, extinguish the flame and let the flask cool. The flask becomes filled with ordinary air which will not have been heated, and which will enter it with all its elements, both known and unknown. As the neck remains open, diffusion will produce incessant exchanges between the air of the flask and the atmosphere outside. Nevertheless, the flask remains indefinitely sterile. How do you explain this result, you partisans of spontaneous generation? There you have organic matter, water, air incessantly renewed, and heat, nevertheless nothing appears in the liquid. You will say that the *genetic power* of the infusion has been altered by the boiling to which we have subjected it. But if, without touching the infusion, I cut off the neck of the flask which contains it, in such a way as to leave it exposed to the fall of atmospheric dust, it becomes clouded in two or three



days. Did the *genetic power* then wait for the disappearance of this swan's neck in order to manifest itself? What is your explanation worth in the presence of this: the curves of the neck, remaining moist at the moment when the fire was extinguished, washed in its passage the air which traversed them in a thin thread? In the beginning when the entrance of the air was rapid, the purifying action of this washing was doubled by that of

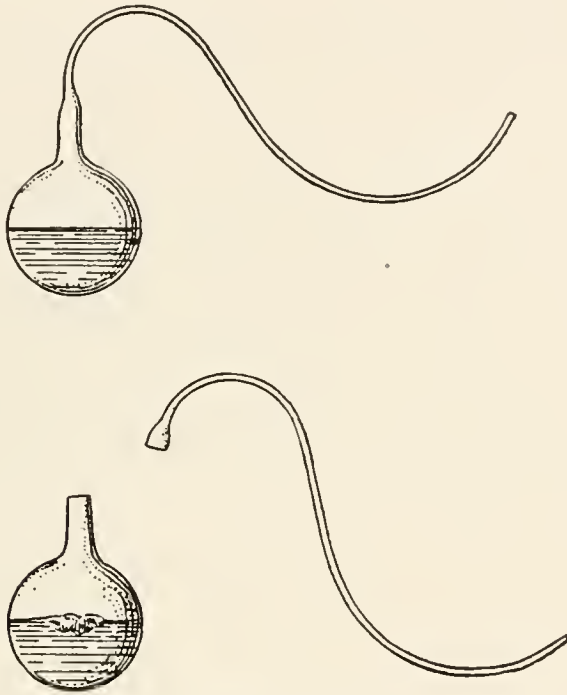


FIG. 12.—Swan-neck flask used by Pasteur in his study of spontaneous generation.

the liquid, still hot and able to destroy the germs which came in contact with it. Later, the wet walls of the neck have held fast the germs of the air as they have passed through the narrow opening. The proof of this is that if you shake the flask in such a way as to introduce into the curve of the neck a little drop of the infusion, having previously closed the open end so that nothing new will enter, this drop becomes clouded, and if you then mix this drop with the rest of the liquid, the latter

becomes populated just as if the neck had been broken off. Another proof is this: when the neck is removed one often sees (Fig. 12) the first development of growth directly under the opening, where the germs from the air have fallen in."

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## V

RESPONSE TO THE ARGUMENTS IN FAVOR OF  
SPONTANEOUS GENERATIONS

"I am not content," Pasteur might have continued, condensing his powerful argument, "I am not content with giving you convincing experiments which always succeed. I do more than that. I explain why my predecessors have so often obtained those contradictory results which have troubled them and stayed their decisions. Thus, always, Schwann and the others have seen their best-contrived experiments fail when they placed their liquids, if only for an instant, in contact with mercury. What imprudence! Is not the mercury constantly and necessarily full of impurities? Those particles of dust which come to it from the air, and which collect on its surface, mingle with it and are carried along with it everywhere. It is for this reason that I have carefully excluded it from all the preceding experiments, which, performed with its aid, might have been easier to carry out, but which might have left us uncertain as to the results.

"And then, to disturb our convictions, there is also the history of this milk which curdles or putrefies under conditions where beef bouillon, the must of beer, and other infusions remain unaltered. There is this yolk of egg, or this meat without water, which we cannot preserve by heating to 100° C. and keeping afterwards in

air which has been heated or filtered through cotton. There are those exceptions which haunted the mind of Helmholtz, of Schroeder and Dusch, and made them admit that there were some 'decompositions of organic matter which needed only the presence of oxygen to start them,' that is to say that spontaneous generation was alone capable of explaining. Very well, there again spontaneous generation has nothing to do with it. Only carry up to 110° C. your milk, your yolk of egg, your meat, and you will preserve them intact as easily as the bouillon. The milk needs to be heated a little more, and that is all there is to it. It is not that it contains more resistant germs, but that it is slightly alkaline, and in an alkaline medium germs are more resistant to the action of heat. The proof is that a decoction of yeast, which is easily sterilized by a short boiling at 100° C. when it is slightly acid, needs to be heated to 105° C. or 110° C. when there is added to it a small amount of carbonate of lime. It behaves then like the milk."

We shall see later that there is in the interpretation of this experiment an error brought to light by Bastian, but which did not invalidate the conclusion, for Pasteur, when he was deceived, had the art of never being deceived more than half way. He approached the mark, when he did not hit the bull's-eye. We shall find a new example of this in the complementary demonstration which follows.

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## VI

### DISTRIBUTION OF GERMS IN THE AIR

There was in favor of spontaneous generation one last argument to which Pasteur had not yet replied. It is the experiment to which we have referred, in which Gay-

Lussac had seen some inert must of grape begin to ferment as soon as he placed it in contact with some bubbles of external air. Men had concluded from this, with some appearance of justice, that there was in each bubble of air something capable of starting all the fermentations or putrefactions which could take place in the most varied liquids in contact with air. This was, it is true, a little too liberal an interpretation given to an experiment which had been performed only twice and had succeeded only once. But if it accorded well with the hypothesis of spontaneous generation which saw in the oxygen the only cause of the appearance of life, it could not accommodate itself to the theory of germs. It seemed difficult that there should be sufficient in each bubble of air to populate the most varied liquids with the most varied microbes.

What degree of credence and of generality could be attributed to the experiment of Gay-Lussac? This was what no one knew, and what Pasteur was obliged to study. It is this part of his work which has attracted the most attention, not that it is the best: all of it is valuable; but this is the most easily understood, and the experiments in it are as simple as they are convincing. Pasteur took again his flasks with a straight neck drawn out. He brought to a boil the organic infusion which they contained, and after having driven out all the air from the interior, through the open extremity of the neck, he closed this at the moment when the steam was given off by melting the glass in the flame of a blowpipe. The flask is thus practically empty of air when it is cooled.

He then took 20 or 40 of these flasks to the place where he wished to make a study of the air, and broke the necks with a long pair of pincers, having first taken the precaution to pass the necks and the pincers through the flame of an alcohol lamp, in order to kill all the germs which

might have been deposited there. Furthermore, throughout the operation he kept the flasks as high as possible above his head, so as to avoid the dust from his clothing. When the necks were broken, there was a hissing sound: this was the air entering. The flasks were then resealed in the flame of a lamp, and carried back to the thermostat.

In some cases, the air which entered contained viable germs, and the infusion became populated with various organisms; in others, the air contained nothing, and the infusion remained sterile. There were always some flasks which remained intact, although each had received from 200 to 300 cc. of external air. To say that there are germs in the air is not, therefore, to say that they occur everywhere, or even that they are very numerous: it is saying that there are some here and none there, that we find more in a low and humid place, favorable to cryptogamic vegetation; that we find fewer in air which is in repose, like that of the cellar of the observatory; that they will be the more rare the farther we go from cultivated land, and the higher we ascend a mountain; that there will be almost none in the midst of the Swiss glaciers where no vegetation can live. Pasteur opened a great number of flasks in the air of these various places, and he always found that some of them remained sterile, and the greater the known purity of the air at the point studied, the greater the number of these.

All the researches made since have confirmed the truth of this conclusion. The air is much less populated with germs than has been supposed, much less, even, than Pasteur thought. To-day men carry on with security, in this regard, either in the laboratories or in surgical wards, operations which they would not have dared to undertake in 1862, haunted as they were by the idea of those germs in the air, to which Pasteur had just called

attention so forcibly. Time was needed to recover from this dazzling fact and to observe more accurately. We shall see Pasteur himself working to harmonize things, and to make that fit into his last theory of the air which his work on spontaneous generation had put into the first. Simultaneously, surgical science developed. After Lister and Jules Guérin, who were preoccupied especially with avoiding atmospheric contagion, came the present day surgery which, neglecting the air, directs its attention and precautions especially to liquids and solids, persons and things, and thus it is that little by little we come into possession of the truth. This work on spontaneous generations has opened horizons whose profundity we do not yet know.

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## VII

### DISCUSSION WITH POUCHET

We must not suppose that this demonstration, as exact as it was, produced universal conviction immediately. It became, on the contrary, the occasion, or rather the pretext, for polemics which did not confine themselves wholly to the scientific field, and from which neither religion nor politics were excluded. The doctrine of Pasteur contradicted certain philosophical doctrines; it spoke to the same purpose as the Bible. In politics, or rather the politics of the time, this was a conservative doctrine; no one has ever been able to understand why. Nothing further was needed to stir up against it certain men and certain journals. On the other hand, scientific men, even the greatest of them, do not always have unbiased minds, or minds fitted to comprehend everything. In short, there was a raising of bucklers, of which the men of my generation have not lost the recollection.

Now that the dust of combat has fallen, it is curious to pass in review the events of the strife, of which, furthermore, Pasteur bore the brunt. We shall discover a Pasteur whom we have not yet known; a vigorous and sometimes a hot-headed polemic, a cautious polemic also, who profits by what his adversaries teach him.

I shall pass rapidly over the long discussion, opened with Pouchet in the first place, then with Pouchet, Joly and Musset. This discussion created a great deal of stir in its time, but science did not derive from it any new truth. In order to obtain a spark, it is necessary to have the friction of iron against flint; here there was only that of iron on punk. Pouchet was a conscientious, erudite naturalist, animated by a desire to arrive at the truth, but impelled by the nature of his mind outside the only paths where it is to be found. He portrays himself exactly in the second line of the preface of his *Traité de l'hétérogénie*, published in 1859. "When by meditation," he says, "it became evident to me that spontaneous generation was another one of the means which nature employs for the reproduction of her creatures, I applied myself to discover by what processes one could demonstrate the phenomena." I picture to myself how Pasteur, as well as Tyndall later, must have read these lines with stupefaction. Thus, behold a scientific man who calls on experiment to prove a truth which he considers in advance as certain—what shall I say—as *evident*, although he has reached it only by *meditation!* How much in accord here are this extraordinary mind and extraordinary language! Tyndall has remarked that it would have required a very powerful bridle to hold in check a mind so strongly biased. Now, not only was Pouchet incapable of profiting by the results of a well-performed experiment, but he was a very mediocre experimenter whenever he left the domain of natural

history and entered a laboratory. We are nonplussed before some of his pieces of apparatus. Thus, for example, he did not hesitate an instant to send a current of water vapor through a drying tube containing pumice stone saturated with sulphuric acid. But aside from these defects as a scientific man, he had, as vulgariser and polemic, some remarkable qualities—a wide knowledge, a boldness of affirmation which betokened a sincere conviction, and a ready pen which wrote without growing weary.

In comparison with Pouchet, Joly, professor of zoology of the Faculty of Sciences of Toulouse, and Musset, head of an institution in the same city, were somewhat lost to sight. Lesser metaphysicians than Pouchet, they seemed quite as incapable of knowing what constituted a well-performed experiment. It was Joly, for example, who, in order to prove that there was nothing living in the scum of dust on the surface of the mercury, introduced what he gathered into water (into distilled water, he said gravely) and was astonished to see nothing appear in the mixture, even when the eye was “armed with the best microscope.”<sup>1</sup> How answer such experiments?

In the laboratory, we had great sport over these details, but the master could not laugh. He would have been wise to repeat philosophically: “We have not the same sort of brain,” but he was indignant to see the truth unrecognized, and contested by such arguments, and to encounter, even in the Academy of Sciences, confrères who hesitated between him and his adversaries. He forgot that science is not univocal, and that one may have a very good mind and still comprehend nothing of a mathematical demonstration, or of the

<sup>1</sup> Examen critique du mémoire de M. Pasteur (Acad. des sciences de Toulouse, 13 mai, 1863).



value of an experimental proof. Fortunately, on his side Pasteur had Balard and Dumas, those confrères whom he still called his masters, although he had already gained the leadership himself.

Balard loved science. He had made very good early progress in it, and his discovery of bromine, made in his pharmacy laboratory at Montpellier, had placed him above his peers. It sufficed to see him in a laboratory managing a piece of apparatus, or making a reaction, to know that he was a chemist to his finger-tips. But he had a certain natural indolence, and he was thenceforth satisfied with his share of glory. To the scientific work which he would have been able to carry on, he preferred that which he found done in the laboratories he frequented. Although each day having the intention of returning to his own laboratory, the next day early he yielded to the desire to see what was going on in the laboratories of his friends. There he wished to see everything, to know all the details, and we told him everything, first, because he had an open mind and a generous soul, then, because it would have been difficult to conceal anything from him: he put into his interrogations at the same time so much shrewdness and simplicity! He admired with all his heart when any one showed him a very nice demonstration! And then, one was sometimes recompensed for this confidence: he would suggest an idea to you, and reveal to you a method. It was he who conceived, by means of the swan's-neck flasks mentioned in the preceding chapter, the experiment designed to show both that there are germs arrested in the neck, and, by introducing into the neck a drop from the interior, that the liquid has not lost its genetic power. We see the drop become clouded and populated, while the liquid in the flask remains unaltered. All these experiments on spontaneous generation trans-

ported Balard with delight and the laboratory became animated with his expansive joy as soon as he entered.

Dumas, more majestic, and at this time a power, came more rarely. He was not desirous of seeing things at such close range. He judged them from his superior height and was no less a very good judge; consequently Pasteur never allowed any of his words to escape him. It was a little in spite of his advice that Pasteur had approached this question of spontaneous generations, and there is no doubt that in giving this advice Dumas was lacking in perspicacity, so much was this study in accord with the mind and the works of Pasteur. But the pupil kept his master in touch with his progress; and he was never more happy than when he recounted to the laboratory some word of approbation from Dumas.

Pasteur had need of these encouragements, for, decidedly, he could not make up his mind to take part in the little war which the partisans of spontaneous generation were pursuing before the Academy and in the journals. But this internal ebullition did not prevent him from being a shrewd manœuverer. Consequently, he allowed the most hazardous affirmations to be made without too much protestation, contenting himself with exposing from time to time the weak points in the experiments which were opposed to his own. He did not wish to follow his adversaries into their own field, knowing that this was dangerous, and that thus they could draw him where they wished: he waited patiently to see them approach his territory. Thus when they affirmed, on the day following some experiments made on the Maladetta, that "wherever they collected a litre of air, as soon as they put it in contact with a liquid capable of fermentation, enclosed in a matrass hermetically sealed, the latter invariably became filled with living germs," on that day, Pasteur made haste to seize

this affirmation on the wing. The experiments on the Maladetta, made apparently under the same conditions as his own, contradicted them absolutely. He demanded that the Academy of Sciences name a commission before which each of the adversaries should repeat his experiments, that commission to say on which side was the truth.

This was in truth a curious episode, and a very instructive one, as we shall see. Requested to repeat their experiment immediately, MM. Pouchet, Joly and Musset, began by demanding postponement until warm weather. The demand was singular: the heat of the thermostat is a perfect substitute for the heat of the sun, and if the doctrine of spontaneous generation is true in July, it ought to be true in December. The commission succeeded, nevertheless, in bringing before it in June all the adversaries in question. We had come from the laboratory of the normal school with everything that was needed to repeat the experiment in dispute: Pouchet, Joly and Musset had come alone and unarmed. It was soon evident that they had no desire to fight. Having tried various dilatory methods, but being brought back incessantly to the question in point by the severe tone of Dumas, and by the slightly mocking pleasantry of Balard—they ended by declaring that they made default and retired.

The battle was won, for Pasteur was sure of his experiments which succeeded once more in the hands of the Commission as an incisive report by M. Balard, inserted in the *Comptes rendus de l'Académie des Sciences*, testified. Had any one told us then that this brilliant victory amounted to nothing he would have surprised us very much. Nevertheless, such was the case. Pasteur was right; but Pouchet, Joly and Musset, were right also, and if, instead of withdrawing, they had repeated

their experiments, they would have embarrassed the Commission very much, and Pasteur would not then have known how to reply to them.

It is in reality quite true that if one opens, at any point whatsoever on the globe, flasks filled with a *decoction of hay*, as Pouchet, Joly and Musset did, it often happens that *all* the flasks become clouded and filled with living organisms. In other words, with this infusion the experiments of Pasteur with the *water of yeast* do not succeed, and one is led to admit that the air which enters into all the flasks carries germs into them.

Let us say immediately that the germs of this air are a negligible quantity, and that any one would obtain the same result by filling the flasks with air sterilized by heat. The fact is that the germs already exist in the infusion. They have resisted boiling, as is the case with a great number of micro-organisms. They have remained inert as long as the flask, sealed during the boiling, remains devoid of air. They develop when the air enters, thanks to its oxygen. But Pasteur did not yet know this fact. Pouchet, Musset and Joly were not any more aware of it, but if they were ignorant of the explanation, they had observed the fact, and if they had been better experimenters, more men of the laboratory, if they had studied more thoroughly the conditions of their success, they would have accepted the challenge, and would have won the battle, or at least each of the adversaries would have retained his own position.

Perhaps it would have been better had things taken this turn, and the Academic commission been obliged to determine that all of the adversaries were right, instead of putting an end to its labors by a bulletin announcing the victory of one of them. Pasteur would

have found that he had been deceived in some particulars, but he was not a man to sulk before the truth, and some ideas which did not enter into science until ten years later, would have found their place there at once to the great advantage of all. We were, in reality, obliged to wait until the contest with Dr. Bastian in 1876 to rediscover them. But the episode is not less curious, when we consider that the passing error of Pasteur had also its good side and its advantages. This is a good illustration of what a series of judgments, revised without ceasing, goes to make up the incontestable progress of science. We must believe in this progress but we must never accord more than a limited amount of confidence to the forms in which it is successively vested. One sometimes reaches the truth by error, and sometimes error by the truth.

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## VIII

### DISCUSSION WITH FRÉMY

Like the preceding, the discussion which opened immediately between Pasteur and Frémy has no interest, even when studied in the light of to-day. I venture to say that it never had any, even when it caused heated discussions in the séances of the Academy of Sciences, it was so incoherent in its diverse phases. When Frémy undertook these studies, he had arrived at an age when the mind does not adapt itself easily to new habits. He had never been good at unravelling problems, and this one demanded much ingenuity and penetration. He had never been familiar with the microscope, nor with the world of infinitely small organisms. One asks then what he thought to accomplish and why he embarked

on this galley. Perhaps he wished only to parade there, for she manœuvered in full sight of the shore. With all his qualities as a man and a savant, Frémy was, in reality, from many points of view still a child. Perhaps he had, notwithstanding, the intention of bringing the ship to harbour, but what an illusion regarding his qualifications for that task! He saw indistinctly and reasoned awry. In order to explain, for example, why Pasteur's flasks with the swan's neck did not become clouded, he conceived the idea that it was due to the vitiation of the air, resulting from the absorption of the oxygen by the liquid in the flasks. This was forgetting the experiments of Schultze, of Schwann, of Schroeder, even those of Pasteur. But this also was nothing. In order to prove this vitiation of the air, which, according to him, would prevent, and consequently would precede, the invasion of the microbes, he cited some air analyses made on flasks already invaded, and where the aërobic organisms had naturally absorbed all or a part of the oxygen. This is unbelievable, and the excellent man truly did not merit, he was so unsophisticated, the bit of harsh treatment which he reaped from his polemic. Pasteur did not treat him as a serious opponent. He was amused at seeing him rush on the sword of his adversary, and the tone which he assumed towards him is well illustrated by the following phrase, written apropos of an Academic discussion in which Frémy, made angry and "driven to the wall" by an experiment of his adversary, had, in order to explain it, and relieve his own embarrassment, conceived the idea forthwith, of saying that "small quantities of grape-must do not ferment," and that there must be a large amount of it for fermentation to take place. Thereupon, Pasteur parried: "In the séance which followed that in which M. Frémy made this declaration in regard to *small quantities which do not ferment*, I

gave myself the malicious pleasure of bringing a large number of very small closed flasks, into each of which I had aspirated a drop of must from bits of crushed grapes. I broke the tapered point of many of them before the Academy, and in all by a sharp hissing, which was heard at a distance, the fermentation of the drop of liquid within was made evident. M. Frémy was present and kept silent.”<sup>1</sup>

It must be said in commendation of Frémy that he did not cherish any ill will because of these thumps, feeling, confusedly at first but more and more clearly later, that his opponent was right. He loved the truth, although he was not always very prompt to recognize it, and when it was necessary to have a treatise written on the ferments and fermentations for the *Encyclopedia*, the publication of which he directed some years later, he went for this purpose not to one of his own pupils, but to one of Pasteur's.<sup>2</sup> No one could terminate a polemic more gallantly!

This discussion, nevertheless, did not remain sterile. There were no sterile discussions with Pasteur, because he always resorted to experiment to combat the arguments opposed to him. He thus found himself drawn into diverse fields, which he would never have approached of his own accord, and, as he had perspicacity, he did not fail to make discoveries therein. Thus it is that he derived from his controversy with Frémy a multitude of curious ideas on the distribution of germs in the air, and germs of yeast on the skins of the grape—ideas which he utilized much later, and which we shall encounter again.

<sup>1</sup> *Études sur le vin*, p. 58.

<sup>2</sup> To Émile Duclaux, author of this book. Frémy's *Encyclopédie Chimique*, Tome ix, 1<sup>re</sup> Section, *Chimie Biologique* Par M. Duclaux. Svo, p. vii, 908. Dunod, Éditeur, Paris, 1883. *Trs.*

## IX

## DISCUSSION WITH BASTIAN

The only discussion which produced fruit in the field in which it arose was that raised by Dr. Bastian. Like Frémy, Bastian had taken up the question a little thoughtlessly, without being very familiar with it, and without any idea of its difficulties. His first experiments were not of any great value; but he had tenacity, fertility of mind, the love of the experimental method, if not an understanding of it, and he has given us ideas, or rather let us say he forced Pasteur to gain ideas, the absence of which had hindered the progress of science. All our present technique has arisen from the objections made by Bastian to the work of Pasteur on spontaneous generations. It was Bastian who made us see that this work which had been so vaunted, abounded in false interpretations, which, he said, invalidated its conclusions. It was Pasteur and his pupils, Joubert and Chamberland, who showed that even if the interpretation had sometimes been inexact the conclusions were none the less well founded.

Bastian's first attack was a blow straight from the shoulder. "You maintain," he said, "that urine boiled and preserved in the presence of superheated air, remains clear and sterile because you have allowed no germ to penetrate there. I say, on the contrary, that the germs have nothing to do with it, and that the sterility of the liquid is due only to the fact that, in spite of all your care and your dexterity, you have not known how to reunite in it the physical and chemical conditions necessary for spontaneous generation. The proof of it is this: if I saturate this urine with a little potash boiled and freed from germs, so as to render the urine neutral,



or a little alkaline, and if I put it, furthermore, not in one of your ovens where it is not sufficiently hot, but at 50° C., this same flask of urine which remains sterile in your hands, becomes clouded at the end of 9 or 10 hours and swarms with bacteria. From whence can they come, if not from a spontaneous generation?"

Repeated immediately in the laboratory of Pasteur, the experiment was successful. It is, in reality, very exact, but what must we conclude from it? Pasteur could not interpret it as Bastian did. He acknowledged that the germs were there: but whence did they come? In this investigation, Pasteur beat about the bush for a long time, and during this time his ideas, like his discussion with Bastian, were rather confused. I will simplify my exposition considerably by saying that these germs for which Pasteur demanded an explanation from experimentation, could be derived from three sources, unsuspected up to that time: first from the solution of potash; second from the boiled urine; and third from the walls of the flask. It was, we see, the introduction of solids and liquids, as conveyors of germs, into a question where up to that time, the air, chiefly, had been incriminated. Let us examine separately the three sources which we have just enumerated.

The solution of boiled potash may contain germs, and yet that seems surprising when one thinks that this solution is made with a piece of fused potash which, in a solid state, actively attacks animal membranes and destroys everything living. Therefore, it is not this which can carry the germs, and, in reality, if we repeat the experiment of Bastian, replacing the solution of boiled potash with an equivalent fragment of fused potash, the experiment does not succeed, and the urine continues to be sterile. Then it is the water that conveys the germs, and in studying this subject Pasteur and Joubert were

in reality convinced that there are germs in all water, even in that which has been carefully distilled, when it is collected in receptacles which have been washed with water containing germs. This fact had already been established by Burdon Sanderson, but the French savants expanded it to a remarkable degree, and stated it more precisely. They also recognized that only the waters from deep sources, those which had undergone in the soil a slow and long filtration through capillary spaces, reached the surface without bringing back the germs which they contained in abundance when they penetrated the soil. They were filtered. We find there all the ideas which have been so useful to us later on the subject of the distribution of germs in water, and out of which was evolved for purposes of sterilization, the Chamberland filter, which has been of such great hygienic value.

Nevertheless, this explanation did not explain everything, and it happened sometimes that when the potash solution had been thoroughly sterilized, or even replaced by an equivalent fragment of potash heated to redness, nevertheless the urine, sterile up to that time, became populated. It is then the urine which supplies the germs: they had not been destroyed by the boiling to which it had been subjected, and thus was introduced into science this very fertile idea that germs could exist in a living state in a nutrient liquid and not develop. Behold the contribution of Bastian! Where Pasteur saw nothing develop, he said: "There is nothing;" Bastian entered the field and said: "Without your knowing it, there is something of which you prevent the evolution." Pasteur retraced his steps and admitted: it is true! but this something is a germ, and if it remains inert, it is because in all living species the first steps in life are the most difficult to make.

At this time, fortunately, Pasteur had already conceived the idea of the spore, the egg of the Infusorian, which demands other conditions for its existence than those with which the Infusorian itself is content. The conditions of this revivification are in general limited, and each species has its own. Because of this fact, and because sometimes these conditions are very delicate, it is possible occasionally for two scientific men who work on the same species to find that they are in disagreement, because of an insignificant difference in their method of work. Because of the fact that the conditions vary with the species, it is clear that these savants will be still more likely to contradict each other if they work, as is almost always the case, on different species, and behold herein a hitherto scarcely dreamed-of explanation of a multitude of contradictions in the experimental study of spontaneous generations.

This element of mystery, now revealed, was calculated to arouse zeal in the laboratory of Pasteur. It was soon recognized there that two conditions govern the rejuvenescence of the germ, the reaction of the liquid and the presence of air. This was especially the work of Chamberland. In a liquid which is too acid, germs heated to 100° C. remain alive, but inert. Diminishing or neutralizing the acidity opens the field for them. This is what Bastian did, and his experiment contained nothing contradictory to the germ theory. It is true that, by way of retaliation, he ought to have recognized the existence of living germs in the flasks which Pasteur regarded as sterile, and from which he deduced evidence against spontaneous generation. But the evidence remained good, although the witness was untrustworthy: heating to 115° or 120° C. the liquids which Pasteur had been content to heat to the boiling point, sufficed to destroy everything that was living therein, and to give

to the experiment entire security, and consequently all its significance. The practice of heating to 120° C. all liquids which are to be sterilized dates from this time. It was the advent of the autoclave into the laboratory.

Air is often another important factor in the revivification of germs, and here it is that we find again the experiment, cited above, of Pouchet, Joly, and Musset. They worked, as I have said, with a hay infusion, obtained by macerating hay in tepid or hot water, which was then filtered and boiled. But this hay contains ordinarily, as Cohn has since shown, an elongated bacillus forming a pellicle on the surface of the infusion when it develops in it, and changing into very resistant spores. It is the famous *Bacillus subtilis* which is everywhere widespread, and owes its ubiquity solely to the fact that it is admirably equipped for the strife, being one of the most *resistant* of known organisms. Its spores, particularly, can withstand several hours of boiling without being killed, but they are the more difficult to rejuvenate the more maltreated they are. If we seal, in a flame, the neck of a flask which contains them, at the time, when the liquid in which they are submerged is boiling, they are not killed, but they do not develop in the liquid when it has been cooled and put in a thermostat, because air is lacking. If we allow air to enter, the infusion becomes populated and this is also the case if we allow only heated air to enter; for the air does not act by introducing germs, as Pasteur believed at the time of the debate before the Academic commission on spontaneous generations: it is its oxygen alone which comes into play.

We see here how necessary ingenuity and discernment are in these matters. Here we have an experiment in which air coming into contact with an infusion brings to it fertility. This was performed by Gay-Lussac with

the must of grape, by Pouchet with hay-infusion, by Bastian with urine. Gay-Lussac concludes: it is the oxygen which has vivified the dead matter; Pouchet and Bastian say: it is spontaneous generation. Then comes Pasteur, who first said: "Not at all; it is germs." Then, when he had been shown that he was deceived: "It is the coöperation of the germs and of the oxygen." The germs always played a part, and in that respect he won his case.

Finally, these germs, so resistant, so widespread, present in all waters, stick to the walls of the receptacles washed with these waters, by a mechanism analogous to that which fixes them in the capillary tubes of a porcelain filter. There they dry, and once dried, they are still more resistant. The heating to  $120^{\circ}$  C. of a flask half full of liquid may sterilize only the moistened part, allowing life to persist in the regions which are not in contact with the liquid. In order to destroy everything, it is necessary to subject the dry walls to  $180^{\circ}$  C. Hence the utility of *flaming* all the receptacles used in microbiology, and behold once more a practice arising like the autoclave, from the laboratory of Pasteur, and which, along with it, established a good technique and made the future secure.

Thus it was that, little by little, knowledge extended and became more exact, and that all the objections to the germ-theory ended in giving us more exact ideas on the subject of the evolution, the distribution, and the characteristics of germs. From this point of view, one may say that all these discussions have been useful because they have given rise to new experiments. The controversy with Bastian was the most useful because there the two adversaries without being of equal force had the same creed and the same faith. Bastian rendered a service to science; he lashed it on its weak side, but he compelled it to advance.







PASTEUR

(Courtesy of Dr. Winford H. Smith, Superintendent, Johns  
Hopkins Hospital.)



FOURTH PART  
WINES AND VINEGARS

I

INDUSTRIAL METHODS IN THE MANUFACTURE OF  
VINEGAR

The theory of Liebig in regard to fermentations, which Pasteur had combatted, was applied also to a category of phenomena to which Liebig had given the name *Eremacausis*, or dry rot, and which were especially phenomena of oxidation in contact with the air. The type to which he referred them by preference was the oxidation of alcohol by platinum black, discovered by Döbereiner. When drops of concentrated alcohol are allowed to fall on finely divided platinum, the mass becomes hot and gives off vapors which have both the suffocating odor of aldehyde, and the penetrating and pungent odor of vinegar. The explanation of the phenomenon is very simple. The alcohol is burned at the expense of oxygen which the platinum holds condensed in its pores. A partial oxidation gives aldehyde; a more complete one, acetic acid; an oxidation still more complete would give carbonic acid, as when alcohol burns with a flame in contact with air. As for the platinum, it remains unaltered.

Such was the type, purely chemical, to which Liebig referred the oxidizing action of the soil on the organic substances which it contains, nitrification, the dry rot of wood, the oxidation of the siccative oils, and, by ex-

tension, the different processes of vinegar-making by oxidation of the alcohol in wine or fermented liquors.

Owing to his study of the different processes employed in his vicinity, since the time of Schutzbach, by the vinegar manufacturers of Germany, he had some right to make this comparison. In a pile of casks with the heads knocked in, and forming a hollow column several meters in height, are piled loosely shavings of beech, over which is showered a feebly alcoholic liquid to which have been added some milligrams of acetic acid and which contains, furthermore, a little acid beer, sharp wine, or some other organic matter in process of alteration, necessary, according to the theory of Liebig, to act as a ferment and set in motion the phenomenon. Under these conditions the shavings play the rôle of the platinum black and do it more economically. On coming into contact with them the alcohol oxidizes, the mass becomes heated, and the pile of casks forms a chimney for a current of air, which, entering below, diffuses throughout the mass, bringing constantly to all points new oxygen, so that the process of acetification progresses rapidly. As with platinum black, there are sometimes formed, in addition to the acetic acid, suffocating products with the odor of aldehyde. Finally, to complete the resemblance, the shavings seem to act only by their presence. After 10 or 20 years of use in the manufacture of vinegar, they are intact, being as sound and clean as on the first day.

We will acknowledge that the comparison was tempting, and will understand that Liebig could not resist the temptation. One falls easily on the side toward which he leans. Pasteur was entitled to look upon the question quite differently. In connection with his studies on spontaneous generation, he had just determined that all organic substances oxidize very slowly in contact with

air when microbes do not intervene; but the acetification in the German process is very rapid. It is true that it was not immediately plain just where the micro-organisms could intervene in this mass of shavings, which always remain unchanged, but there was something which resembled it in the factory of Orléans, a village which, for a long time, has had a merited reputation for its vinegars.

There they carry on operations in casks lying on end in piles and filled about two-thirds full of a mixture of unfermented vinegar and fermented wine. Now, on the surface of the liquid, in the casks which behave properly, there is a fragile pellicle which the vinegar-maker takes great pains not to disturb and not to submerge, because he considers it a precious ally. Experience having taught him that it needs air, he has opened for it a large window in the top end of the cask, above the surface of the liquid. He watches this pellicle and cares for it. As long as it remains spread over the surface of the liquid, all goes well; if it is broken and falls in fragments, all is lost. It is then necessary to produce a new one; and sometimes, God knows, with how much trouble, expense and groping about! A blast of heat, a blast of cold, may suddenly interrupt all manufacture.

What then is this pellicle which is so precious and so delicate? Pasteur had been asking himself this question for a long time, but he only felt himself ripe for the study of this question after he had carried out his studies on the nutrition of micro-organisms and on the spontaneous generations which we have reviewed. He was henceforth armed and equipped, and less than a year sufficed him to make on this subject one of those researches *à la Lavoisier*, which immediately become classic because of their fullness, their elegance and their simplicity.

## II

## THE MYCODERMA OF VINEGAR

As Pasteur had thought it out, all the work of oxidation was performed by a micro-organism differing from those with which he had been familiar up to this time, in that it is an agent for the transmission of the oxygen of the air to certain substances. These functions make it necessary for it to live in contact with the air on the one hand, and with the nutrient substance on the other, and it develops on the surface of the liquid in the form of a delicate veil, smooth and level at first, later in folds, because, when the organisms become too crowded, it is necessary for them to pile up on each other. This form of veil won for this organism the name of *Mycoderma aceti*, or the mycoderma of vinegar.

Three things were remarkable about this organism. In the first place, its marked aërobic character. It was the exact antipode of the butyric vibrio, previously discovered, and it was to characterize the two so opposite functions of these two organisms that there were created with the collaboration of Chassang, professor of Greek in the École Normale, the two words *aërobic* and *anaërobic*. The acetic ferment was also singularly prolific. In 24 hours, it would cover the surface of a vat of any size whatever, with a fine pellicle of cells crowded together, provided that one sowed here and there some cells, as seed. These form islands which become joined in a continuous layer. The cells of the ferment are almost twice as long as broad (5, Fig. 8). It takes 400 of them placed end to end, or 800 placed side by side, to make a millimeter. That makes a minimum of 30 millions of cells to the square centimeter, or 300 thousand millions of cells in a vat with a surface of a square

meter, covered in 24 hours. The ferment best known up to that time, the yeast, gave figures much smaller and less striking.

This is not all, for we are about to see appear a new conception, which the future will make productive—the conception of the *fermenting power*. These 300 thousand millions of cells weigh about 1 gram and can acidify in 4 or 5 days, when the conditions are favorable, 10 kilograms of alcohol. That is to say, each one of these cells demands per day two thousand times its own weight in food material. And here there is raised one of the corners of the veil which for so long a time has masked from us the grandeur of the rôle of the infinitely small organisms. Their power of work is out of all proportion to their weight. With a feeble volume, they can produce great effects: we understand that they may occupy a great place in the economy of the globe and yet pass unperceived.

The oxidation of these 10 kilograms of alcohol requires the putting into play of more than 6 kilograms of oxygen; that is to say, more than there is in 15 cubic meters of air. We explain thus the utility of the current of air ascending in the column of shavings in the German method, and of the large open window in the upper end of the Orléans casks.

This oxygen, which it derives from the air through its aërial surface, the mycoderma transmits to the alcohol through its submerged surface. But oxidation does not always take place in the same way. Sometimes it is arrested in the aldehyde state and the organism yields products with a disagreeable and suffocating odor. As in case of the oxidation due to platinum black, the process is arrested half way. At such times the organism lives with difficulty; it suffers. Why should we not say that it is sick? Disease and death are the natural

attributes of life, but the idea of disease in a creature so small, was none the less original. It was the first time that it had presented itself. Since then, it has been greatly developed.

On the contrary, sometimes this ferment, instead of being arrested half way, goes beyond the acetic acid stage, exactly, again, like the platinum black, and instead of acetic acid, yields water and carbonic acid. Then it consumes the acetic acid which it has formed, and here again we have the first example of the ability of a living organism under certain conditions to destroy a product which under other conditions it has manufactured. The organism consumes the acetic acid when there is no alcohol at its disposal, that is to say, it consents, when it is starving, to touch a food which it scorns and rejects in other circumstances, and which thus has accumulated in the ambient liquid. But this acetic acid is its second choice of food, and it abandons it in favor of alcohol as soon as it has the opportunity.

Curious, is it not, this choice of food in the world of infinitesimal organisms! What prevents us from seeing therein an act of volition or of instinct? Observe that it is an entirely different thing from finding that each organism has its own food material, that the yeasts, for example, can obtain nourishment only from sugar. The acetic ferment can make a choice, and show preferences: it has free will. I know well that it is governed by its needs, but how many acts of volition have as a cause, though often obscure, only that of satisfying needs? Let us not insist upon this point, however, but confine ourselves to noting with what care Pasteur sought by their study, as soon as micro-organisms had brought him into contact with life, new light on the physiology of the higher organisms. He did not fail to compare his acetic ferment, the agent of oxidation, with the red cor-

puscles of the blood, which are also charged with transporting oxygen to the tissues, giving it up to certain substances in preference to others, thus carrying on the oxidation that is needed, even if it is not voluntary and premeditated. He had asked himself what would happen if the red corpuscles should become diseased in the same way as the cells of the acetic ferment, arrested in their development in the aldehyde stage of oxidation. In short, he penetrated through his micro-organisms, into the laws of physiology and pathology.

The practical consequences of his discoveries equalled their theoretical promise. They restored security to the Orléans vinegar manufacturers, who were henceforth masters of the mycoderma veil in their casks instead of being subject to its demands and caprices; they made it possible for the boldest of these men to adopt a new method of manufacture whereby, instead of leaving intact for a long period the pellicle formed on the surface of the liquid, they resowed it and renewed it at frequent intervals. Thus not only could one make more rapid progress, but could regulate the production to the demand, whereas, by the old Orléans method production must be going on constantly and the casks could not lie idle, lest they should become inert.

But is it only in the Orléans process that the microbe intervenes? Not at all. We find it also in the German process, but it is less apparent there, because it is formed in much less quantity. In Orléans, the white wines, rich in organic matter, are used especially for vinegar-making, and the layer which develops on the surface of the liquid in the casks forms thereon sometimes a thick veil. In Germany, little else is used for vinegar-making except alcohols diluted with water and mixed with that small quantity of wine, or sour beer, which Liebig demanded. This liquid is not very nourishing and seems

unsuitable as food for even the least exacting micro-organism; but it is sufficient, and if one scrapes with the point of a knife the surface of these beech shavings, which seem so sound and clean, he finds there a transparent pellicle formed of cells entirely similar to those in the Orléans casks. The manufacture of vinegar is then everywhere due to bacterial action.

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### III

#### DISCUSSION WITH LIEBIG

This conclusion was not calculated to please Liebig, who was defeated on his own ground, and on a question where the close analogy between the industrial results and those furnished by platinum black seemed to rule out all physiological action. An old champion such as he could not yield without fighting, and he retaliated with two memoirs, the one *On fermentation and the source of muscular energy*,<sup>1</sup> read before the Royal Academy of Sciences of Munich in 1868 and 1869, the other<sup>2</sup> inserted in the Proceedings of the Bavarian Academy in 1869. Both demonstrate how difficult it is for even the most eminent scientific man to adapt himself in his old age to new ideas, when they run contrary to the current of those in which he has passed his life. Experience and erudition are then a restraint: one must shed his old skin and abstract himself from all that he has learned.

As the title of the first of these memoirs indicates, Liebig enlarged the scope of the debate and returned to the question of alcoholic fermentation in search of

<sup>1</sup> Ann. de ch. et de phys., t. XXIII, 4<sup>e</sup>, sé. p. 5.

<sup>2</sup> Ib., p. 149.



light on the physiology of the cell. We shall not follow the discourse in all its developments, which are sometimes digressions, but shall ask only what it had to reply to the new doctrine on the fermentations.

On this point his position became more and more embarrassing. Already, at the time when he had first developed his theory, he had been obliged to admit that the yeast was a living organism which renewed and destroyed itself continually, and it was only the products of the destruction which made the sugar ferment. That point had become difficult to maintain and support after Pasteur had shown fermentation to be a cellular phenomenon. It is curious to see how Liebig extricates himself from this difficulty. He considers that life is accompanied at every instant, in every cell, by a movement of decomposition and reconstruction, and, naturally, it is to the first that he has recourse. He admits then the physiological phenomenon but he takes into consideration only a part of it and, once more, the chemical side, endeavoring "to reduce the chemical decomposition of the sugar to a simple formula common to all analogous phenomena."

The attempt is bold, and we recognize in it the generalizing mind of Liebig. We shall see how he succeeded. Let us note in the beginning that, from a chemical point of view, the vital phenomenon of Pasteur does not differ essentially from the phenomenon of movement of Liebig, and that it is possible to reconcile them. "I admit," says Liebig, "that the yeast consists of vegetable cells which come into existence and multiply in a liquid containing sugar and an *albuminoid substance* (it is I who underscore). The yeast is necessary in order that there may be formed in its tissues, by means of the albuminoid substance and the sugar, a certain unstable combination," which alone is capable of undergoing dismemberment.

When the yeast ceases to grow, "the union between the constituent parts of its cell-contents is destroyed, and it is through the movement that goes on there that the cells of the yeast cause a derangement, or a separation, of the elements of the sugar, or of other organic molecules."

And behold how, even in the sciences, that is to say where one is dealing only with facts, one can always marry the Grand Turk and the Republic of Venice. Liebig made a concession of words on condition that his opponent would make to him a concession of facts. "I grant you," he said, "that this is a vital phenomenon taking place in a living organism, provided you grant me that it is of a chemical order. If you do not make this concession, I shall always have the right to say that you have not looked into the question far enough, that you have been arrested before a closed door which I am trying to open." The curious thing is that, fundamentally, he was right; that the term *vital phenomenon* which Pasteur resolved upon, was in no sense more exact than Liebig's phrase *molecular disintegration* (d'ébranlement moléculaire); that, furthermore, all phenomena of nutrition within the cell are reduced necessarily to chemical phenomena. But the value of a theory lies not in the words which express it, all of which are necessarily somewhat vague; otherwise, absolute truth and clearness would be reached on a question, and we shall never arrive at that. The value of a theory depends upon the direction which it gives to research. If Liebig was perhaps right in affirming that within the cell, in the deep roots of the vital act, his theory and that of Pasteur were blended, one is astonished to see him ignore or forget that they are essentially distinct from the point of view of research and progress. The one theory affirms the specificity of the act of fermentation and incarnates it in a living organism, which can

be cultivated and transferred from medium to medium with its specific properties. The other theory denies this fertile specificity, since it admits again in 1869, as we have just seen, that the cells of the yeast can separate "the elements of sugar or of other organic molecules."

These two memoirs of Liebig were translated and published in 1871 in the *Annales de chimie et de physique*. I cannot surmise what procured for them the honor of this exhumation. Pasteur was taken by surprise, and replied in the *Comptes-rendus de l'Académie*. The war of 1870 had just ended, and his soul was embittered. He did not consider at all in these memoirs the special pleading, or dissertation, on origins and causes. He went straight to the facts. Liebig had had the imprudence to gainsay some of those facts which troubled him. He would not have it, for example, that the yeast could develop, live and produce fermentation in a medium containing only sugar, mineral salts and ammonia, as the exclusive source of nitrogen. The last dress given to his theory demanded in addition to these, as I have emphasized above, a previously elaborated albuminous compound.

In this respect I find it very difficult to come to terms with Liebig. While he was on the scent of philosophical explanations, he could just as well have admitted that the yeast itself manufactured in its own tissues the albuminoid substance of which it had need. I do not see wherein this conception stood in the way of the final development of his theory. But he had his idea, which the experiments of Pasteur contradicted. He, therefore, had repeated this experiment of fermentation in a mineral medium and had not succeeded, because it is difficult, and had concluded that Pasteur was deceived.

He denied, furthermore, that *Mycoderma aceti* was the

agent of acetification in the German vinegar works; "for," he said, "on a wood shaving which had been used for 25 years in a large vinegar factory in Munich, there was no trace of mycoderma visible, even under the microscope."

In the presence of these denials, Pasteur had recourse anew to the tactics which had proved so successful with Pouchet, Joly and Musset. He demanded that Liebig present himself, in company with him, before a commission of the Academy of Sciences, which should be charged with the duty of pronouncing between them, and in the presence of which Pasteur offered in the first place to prepare, in an exclusively mineral medium, as much yeast of beer as Liebig could reasonably demand; in the second place he promised to show to the commission, and to Liebig himself, the acetifying mycoderma on all the beech shavings of the factory in Munich.

The challenge was urgent. Pasteur would not have been in position to give it at the time of his studies in 1860 on alcoholic fermentation. His cultures of yeast in a mineral medium were at that time too poor and too uncertain, but since he had begun his studies on beer, to which we shall soon refer, and had found yeasts accommodating themselves to these mediocre culture conditions, he was sure of his facts. Liebig did not accept the challenge. He only remained a little melancholy.

I have as proof of this a letter in which he states the somewhat fallacious idea, that by going into the subject thoroughly enough, Pasteur and he would have ended by discovering and understanding each other. "I have often thought," he wrote me in 1872, "in my long practical career and at my age (69 years), how much pains and how many researches are necessary to probe to the depths a rather complicated phenomenon. The greatest difficulty comes from the fact that we are too much ac-

customed to attribute to a single cause that which is the product of several, and the majority of our controversies come from that.”

“I would be much pained if M. Pasteur took in a disparaging sense the observations in my last work on fermentation. He appears to have forgotten that I have only attempted to support with facts a theory which I evolved more than 30 years ago, and which he had attacked. I was, I believe, in the right in defending it. There are very few men whom I esteem more than M. Pasteur, and he may be assured that I would not dream of attacking his reputation, which is so great and has been so justly acquired. I have assigned a chemical cause to a chemical phenomenon, and that is all I have attempted to do.”

Thus Pasteur and Liebig, two master minds, each qualified to grasp the view-point of the other, both of whom loved science above all things, remained divided, because they could not agree on the rôle of the yeast in alcoholic fermentation. Is there not to be derived from this a great lesson for scientific men, and even for those who are not?

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#### IV

#### THE DISEASES OF WINE

We shall perceive at once the advantage of having the theories of Pasteur replace those of Liebig in science. Arrived at this stage of advancement, Pasteur had before him a fertile province which he could conquer by a wave of the hand, and which would have remained closed and inaccessible under the old ideas. I will explain my meaning.

What had Pasteur just found out? That acetifica-

tion, that is to say one of the *maladies* to which wine is constantly exposed, is exclusively the work of a micro-organism. But there are many other diseases which invade wines with more or less rapidity. The wines of Bordeaux *turn*, those of Burgundy become *bitter*, the wines of Champagne become *ropy*. At this time, the Phylloxera had not yet made its appearance, and many persons had *caves*; but there was no cave where a malady of the wine did not appear from time to time, and did not cause losses, which were often grievous.

Upon that point, the ideas of Liebig shed no great light. According to them, the wine was constantly in movement, at work; those wines which preserved themselves intact, and were called *de garde*, reached the end of fermentation with a certain state of equilibrium between their sugar and their organic matter serving as ferment; these two elements were equally exhausted. If there had been too little ferment in the beginning, a portion of the sugar remained unchanged, and the wine was sweet, that is to say incomplete. If there had been too little sugar, on the contrary, some ferment remained which continued to work upon the substance and to produce therein vitiations of the taste. This explanation, so beautifully symmetrical, had seduced people's minds, and the reader found it paraphrased in all the books on the subject. As to a remedy, it did not give any, or at least it had not done so.

For Pasteur, on the contrary, these ideas had no meaning. He was sure that the activity of the yeast was arrested after having transformed the sugar, and that it could act neither upon the alcohol which it had formed, nor upon the other elements of the wine. In that he was deceived, for we have seen since that the yeast can destroy in time the glycerin which it has produced, just as the mycoderma of the vinegar burns the

acetic acid which it has formed. But, as usual, Pasteur was deceived only half way, and his deduction was exact. The vitiations in taste which sometimes are observed in certain wines could not result from any normal physical or chemical phenomenon, for the wine was preserved almost everywhere in the same fashion, and these changes ought to be seen everywhere. There remained then one plausible explanation, that is that these vitiations came from special fermentations, produced by special ferments analogous to the acetic ferment.

Here is the conclusion to which the logic of his mind and of his acquired knowledge led Pasteur! It remained to see what experimentation would show. He had at Arbois, fortunately, some old comrades of his childhood who owned some caves well stocked for home and market purposes, and he easily obtained permission to subject their wines to a microscopic study.

From the first moment, he surmounted the difficulty. Every time that the tasters pointed out to him a particular defect in taste, he found so constantly a distinct microscopic species mixed with the yeast in the bottom of the cask, that soon he was able to make the test inversely, that is to say, to indicate in advance the savor of the wine by examining its deposit. The normal wines contained only the yeast.

With a guiding idea, so clear and so well verified by experiment, he could begin. After some months passed at Arbois in an improvised laboratory, Pasteur succeeded in elucidating the question, and, in 1866, he was able to place in the hands of the Emperor, who had encouraged him in his researches, a book containing the complete solution of the problem which he had set himself to solve.

This book is a trilogy, of which all the parts hold together. In the first part, he shows that all the maladies enumerated above, the *turning*, becoming *bitter*, becom-

ing *oily*, which are not the sole changes which wine can undergo, but only those best known, are each dependent upon a special micro-organism which lives at the expense of one of the elements of the wine, and imprints on this beverage a characteristic change of composition and of taste. This is not the place to insist on the morphology or the properties of these different organisms represented in Fig. 8, page 70. We will take from the history of the facts only what is necessary to explain the history of the ideas.

The solution of this first problem allowed two others to be approached. What goes on in a wine which becomes old normally, in the absence of organisms? What is it necessary to do, in order that wine may always grow old normally? It is on these last two questions that some developments are necessary. I would like to show to what degree the new manner of regarding them and of treating them rendered them fertile.

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## V

### ACTION OF OXYGEN ON WINE

In the way in which it was stated, the first question was evidently one of pure chemistry, and Pasteur found himself brought back to his first domain. The natural aging of a wine, when microbes are absent, can only take place by the play of forces within the liquid, and of those which may result from its contact with oxygen. What did science and practice have to say on this subject?

The practical man seemed to be inspired with a terror of the oxygen of the air. The wine was exposed to the air only so long as absolutely necessary for the decanting. It was the custom to *sulphur*, that is to say, to fill with



sulphurous acid the casks in which it was to be received; also, in some portions of the country, to *fill*, that is, to keep constantly full, the casks in which it was stored. It was said that it is more exposed to the danger of spoiling in casks of permeable wood than in glass bottles. It was well known that it became flat in contact with the air, and recently M. Berthelot had quite justly related this phenomenon to an absorption of oxygen. Bous-singault had shown, on his part, that the wine of casks contained only nitrogen and carbonic acid, that is to say, there is no longer a trace, in the free state, of the oxygen which it has certainly taken from the air at the same time as the nitrogen. In short, for science as for practice, wine seemed to be a substance most oxidizable and unstable in regard to aëration.

Of that there was no doubt. Pasteur had a great respect for secular practices and said that science ought not to condemn them lightly, but that it had always the right to search for their interpretation. It might be that the wine was really unable to endure contact with air, but also it might be that air is necessary to the microbes which menace the wine, and that to deprive it of the air would, in a measure, guarantee it against disease.

Pasteur had already arrived at a stage where he could accept only the second of these two interpretations. He knew from his experiments on spontaneous generations, how little organic substances are oxidizable without the intervention of microbes, and on the other hand, he had just seen that the acetic ferment which constantly threatens wines with acetification has great need of oxygen. Furthermore, while he was studying this mycoderma of vinegar he had also studied another superficial pellicle, that which forms so easily on the surface of wine left behind in filling the bottles and which resem-

bles the preceding in its need of oxygen—the mycoderma of wine.

The latter, although it is more frequent than the mycoderma of vinegar, nevertheless has less grievous effects, because, not stopping half way, it pushes quite to term the oxidation of the alcohol, and makes out of it immediately water and carbonic acid. This carbonic acid replaces the oxygen absorbed from the air, and by reëstablishing the pressure, prevents a new influx of air and of oxygen. Thus the development of the mycoderma of the wine, which takes place on the surface of all the casks which are not *full*, ordinarily passes unperceived, although sometimes the layer which covers the liquid may be thick. When it has exhausted all the oxygen which exists above it in the closed cask, it renews its supply only slowly; and when this happens it consumes it entirely and leaves no trace of it, in a free state, in the liquid below. It is an impenetrable filter for the oxygen, as impenetrable as a wall of glass.

That granted, did the practices employed in wine-making favor the wine or its parasites? In examining the question from this entirely new point of view, Pasteur was not slow in recognizing that, far from being formidable to the wine, it is the oxygen which *makes* it, which takes away the acid and rough taste of new wine, and which makes it more and more fit to drink. It is also the oxygen which divests it little by little of its coloring matter, yellows what is left, and gives to it gradually that onion-skin tint, with which our ancestors were familiar, and of which we are ignorant, because they knew the worth of life, and we know only its cost. Finally, as its action increases, the oxygen, after having given to the wine the taste of old wine, ends by consuming it and spoiling it. When he had studied a subject Pasteur loved to sum up the ideas which he had ac-

quired in the form of some startling experiments which at the same time furnished a verification of his ideas, and constituted a classical demonstration. Here are some which were used to *illustrate* this subject.

Suppose at the end of the fermentation, at the time

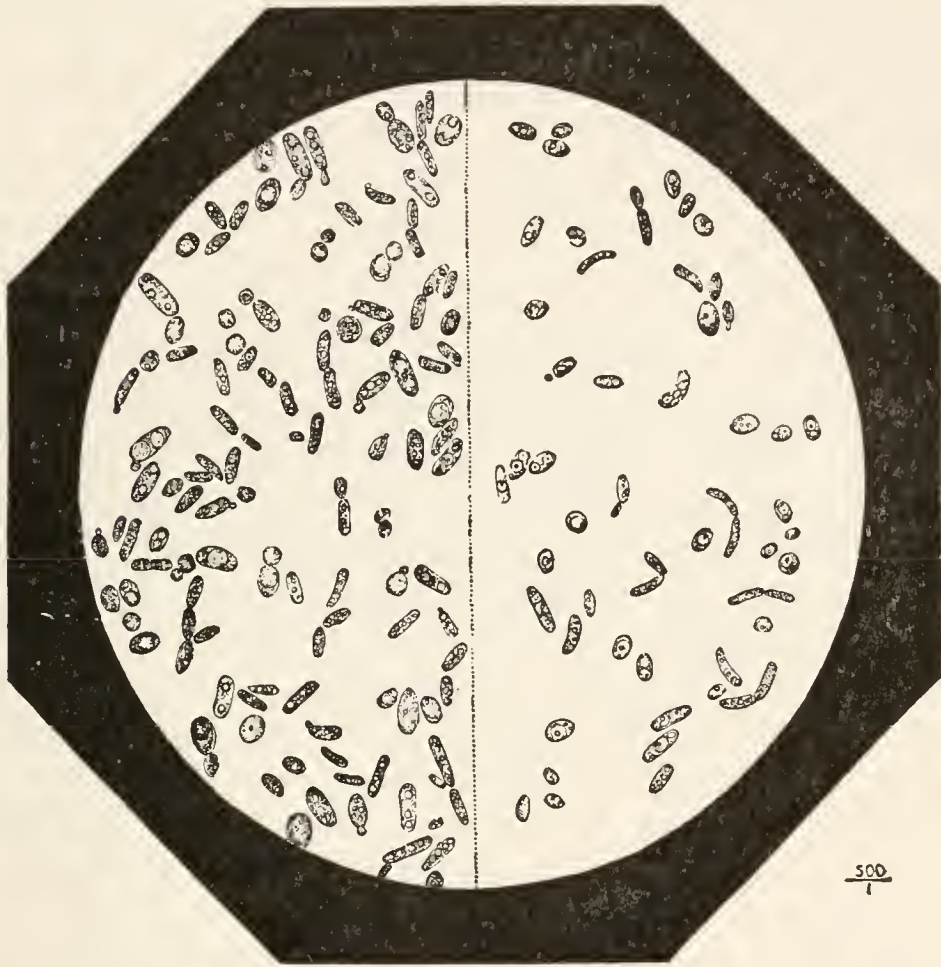


FIG. 13.—Mycoderma of wine.  
Submerged. In the state of flowers of wine.

when the wine, already clear, is still saturated with carbonic acid, we fill a bottle full in such a way that at no time during the process does the wine come into contact with the air. This operation ended, the bottle is hermetically sealed by melting wax over the stopper. The wine thus treated remains indefinitely as it was at

the moment of drawing off; it preserves its color; its savor does not change to any appreciable degree; it takes on no particular bouquet; it is always *new wine*. During this time, the rest of the same wine, preserved in a cask and subject to the ordinary manipulations, *becomes old* in the complex sense which one ordinarily gives to this word. What differences are there then between the two wines? One only: under its envelope of glass the former has not been subject to the action of the oxygen of the air which filters constantly and slowly through the barrel staves, and which, combining with the wine, determines its ripening.

Without taking any particular precautions to avoid excess of air, let us repeat the experiment which I have just described, leaving the bottle half empty and closed with its stopper. While the wine in the previous experiment remained *young*, that in the new bottle clouds and gives an amorphous deposit which increases little by little and finally adheres to the walls. It is the red coloring matter which has separated from the wine. At the same time, the oxygen left in the bottle disappears, and the wine changes, loses its original savor, becomes old, and takes on in a high degree the taste of *rancio*,<sup>1</sup> if it is red, of *madeira* if it is white. It may even fade away and disappear altogether, if there is too little of it in proportion to the oxygen.

The essential act in the aging of wine is, therefore, its slow combination with oxygen. When the absorption of oxygen is too rapid, the wine becomes *rapid*, but this is a passing phenomenon, and it is often sufficient to let the wine alone for this taste to disappear, as soon as the oxygen absorbed in a gaseous state has served in the wine for the oxidations which have consumed it.

<sup>1</sup> Old wine which has acquired the taste of Spanish wines. "rs.





PASTEUR

(Courtesy of Dr. Winford H. Smith, Superintendent, Johns  
Hopkins Hospital.)

## VI

## THE HEATING OF WINES

These facts being formulated and established in the first two parts of the *Études sur les Vins*, the third part appears as a dénouement. The diseases of wine are correlative with the development of parasitic vegetations; it is the fear of these parasites which burdens all the practices of wine-making and the preservation of wine, and forbids the employment of other methods more favorable to the aging. If we can succeed in eliminating these dangerous ferments, or in destroying them when they are present, we shall have overcome this antinomy and have solved the problem.

It is here that Pasteur found once more the advantage of his earlier studies, for it is remarkable that, save from himself, he borrowed almost never. We have seen this in what precedes. It will be still more apparent as we advance.

The problem was to prevent or to arrest the development of the parasites without in any way changing the constitution of the wine. For this purpose he had at his disposition the action of antiseptics or that of heat. He tried antiseptics first, especially the hypophosphites and the bisulphites of the alkalin metals, which are without decided odor and taste when they are in dilute solution, and which become inoffensive phosphates or sulphates after having absorbed oxygen. The results were mediocre or negative. It was then that he thought of the action of heat.

We understand his hesitations in having recourse to this agent. By means of it he was sure of killing the microbes without even heating to the boiling point, for wine is an acid liquid, and the acidity helps on the

action of heat, as we have seen when considering spontaneous generations. Moreover, there was a chance, and Pasteur had not failed to perceive this possibility, that it might not be necessary to kill the ferments, which, considering the slowness with which they ordinarily develop, are under unfavorable conditions in the wine. To weaken them by the heating so that they could not multiply would perhaps be sufficient. All this was encouraging. But, on the other hand, the employment of even a minimum quantity of heat appeared to have its grave dangers. Everybody has drunk warm wine and knows that it is no longer wine. Those ancestors whom we invoked a short while back recommended one to drink *cooled* wine. Only Bordeaux wine, they added, is improved by conveying it into the dining room four hours in advance of the guests.

Yes, Pasteur might have replied to these objections: but all those wines which one hesitates to heat are wines recently drawn off and aërated. Would it be the same for the bottles which would be heated only after having allowed their contents time to transform into combined oxygen the gaseous oxygen absorbed during the racking? No one could reason more correctly, and it is thus that Pasteur, at the first step, and almost without groping, by proceeding always in the direct light of his former experiments, reached that procedure of heating to  $55^{\circ}$  C. for which such a noble future seemed reserved when it first appeared.

At this time, in 1867, the prosperity of viticulture was great; France reckoned more than 2 million hectares planted in vines and her wines, the dissemination of which was favored by commercial treaties, seemed destined to reach all the markets of the world. To give to an industry operating upon 50 million hectolitres, and worth 500 million francs, the means of avoiding



the deterioration of its merchandise and of increasing more rapidly its commercial value, was a public benefit.

Unfortunately, two years previous, on the plateau of Pujaut in Gard, there had appeared the Phylloxera which has since caused so much devastation, and the following year the insect had disseminated its colonies over a large portion of the departments of Vaucluse and Bouches-du-Rhône. Another microbial power had taken a hand, against which science and agriculture were at this time unarmed. Consequently, for some years Pasteur's method was ruined. No one need consider how to keep grains in a time of famine, and the heating of wines was little practised except for those which must be shipped under bad conditions as to keeping, for example, in the commissariat of the Navy.

But now they return to it gradually in the wine industry, and for some years it has been employed regularly in the beer traffic, with the best results. It has done more, it has entered into the language, and the word *pasteurize* signifies, even outside of France, to protect against microbes by the action of heat. We pasteurize wine, milk, and beer, and are right in performing the operation, and in so calling it.

I would be through with the subject if it were not for saying a word or two on the claims of priority raised against Pasteur, and on the somewhat bitter polemic which resulted. It is always wrong to confide one's rancors and jealousies to the public. We do not recollect sufficiently that this public has its own affairs, is only moderately interested in the fundamentals of the debate, and contents itself with being amused at the blows. Pasteur had the best side here and should have been content with shrugging his shoulders. He was accused of having re-invented the process of Appert, as if there could be the least parity between the empiricism of the

one and the experimental logic of the other. Appert had taught us only one thing, viz., that sometimes wine could be warmed without changing the taste, or becoming *heated wine*. If Pasteur had known of this experiment, he would have hesitated less than he did in having recourse to the action of heat, but his work would have remained the same. Besides, he made haste, as soon as he knew of them, to render to Appert's experiments the credit they deserved.

It was also said to him, in all manner of ways, that the heating of wines had been known and esteemed for a long time at Mèze, in the department of Hérault, near Cette. "So be it," answered Pasteur, who had gone to see, "they do warm the wine at Mèze, but it is to age it more speedily. For this purpose they warm it in contact with the air, for a long time, so as to bring about changes in taste, which sometimes exceed the limit, and which it is then necessary to correct; these gropings about in the dark show that the wine merchants of Mèze do not have any clear idea of what they are about, and have not read my book. It would be to their interest to do so, for I give the theory of their practice. Meanwhile, what has this long and dangerous warming in contact with the air in common with that rapid heating to 50° C., protected from the air, which I recommend?"

There remains finally the laggard claim of M. de Vergnette-Lamotte, but this is so strange and shows such ignorance of the subject, that it is better not to speak of it. It resulted in some bitter-sweet notes which may be read in the *Comptes rendus de l'Académie des Sciences* and in the *Moniteur scientifique de Quesneville*. All profound faith is necessarily a little intolerant, and Pasteur had that faith.





PASTEUR

(From a woodcut in "Jour. d'Agric. pratique," 1895.)

## FIFTH PART

### STUDIES ON THE DISEASES OF SILKWORMS

#### I

#### ORIENTATION TOWARDS PATHOLOGY

I still recall the day when Pasteur, returning to the laboratory, said to me with some emotion in his voice: "Do you know what M. Dumas has just asked me to do? He wants me to go into the South and study the disease of silkworms." I do not recall my reply; probably it was that which he had made himself to his illustrious master: "Is there then a disease of silkworms? and are there countries ruined by it?" This took place so far from Paris! and then, also, we were so far from Paris, in the laboratory!

However that may be, Pasteur had reached one of the turning points of his life. For a long time he had had a presentiment that all the new ideas he had introduced into science might be of importance for the physiology and pathology of the higher animals. For a long time the two notions of fermentation and disease had been connected, as we have seen during our consideration of spontaneous generations. But this relation had become closer since it had been known that it was living cells which presided over the processes of fermentation. However, let us keep from believing that the logic of the ideas of Pasteur led him, at this time, to the spot where we see him so naturally to-day, namely to the conclusion that disease could result from the development, in the normal tissues, of a living microscopic organism,

the cause of the disease. That is the idea divested of all its trappings—an idea reached ordinarily only after one has made the tour of ideas much more complicated. In fact, as we shall see, Pasteur reached this conclusion only, so to speak, in spite of himself, and after two years of study.

He was, it seems, more disposed to believe at this moment that the disease, whatever it might be, could by modifying the fluids of the body prepare the soil for this or that microbe, which was then according to the case, either the result of the disease, or the visible evidence of it, or the beginning of a new disease. We shall see later that these notions are not as exclusive of the other idea as one might at first sight believe them to be. In all cases, they ended with a repercussion of the microbe on its host, and it was for this reason that Pasteur maintained for so long a time the relations between the physiology of the ferments and that of the higher animals. Thus we have seen him liken the red blood-corpuscle to the acetic ferment which, like the latter, can take the oxygen from the air and carry it, endowed with a more powerful activity, to the combustible substance.

But when there was raised the question of going farther and of actually coming into contact with the higher animals, Pasteur hesitated. He was not a physiologist. To no purpose did we go to hear the course of Claude Bernard, where he took notes feverishly. It would have been necessary for him to become a new soul, and he had neither the time for it nor the patience. The insistence of Dumas had just placed him face to face with an experience which he both desired and dreaded, and if his self-distrust had made him hesitate, at the first encounter, in reality, the attraction for the unknown and a certain interior voice urged him to accept.

Consequently, his decision was soon made. After

having acquired a fragmentary knowledge of the general structure of the larvæ of insects by causing to be dissected in his presence a white worm [larva of the May beetle] or a larva of *Oryctes nasicornis*, after having assisted at some sittings of an *Imperial Commission on Silk Culture* from which he came away more discouraged than enlightened, after having skimmed the last published books on the subject, he set out for the South. It was at the beginning of June: the cultures of the silkworms were almost completed. From this fact he might have plead for more time and the putting off of his investigations until the following year, but his master, M. Dumas, had spoken: he was also more eager than he himself suspected to enter into this new world, and he desired to begin the work at once.

To it he devoted six years, which it will not be unprofitable to describe in detail, and that for two reasons. The first is that nothing can be more curious than to see Pasteur at close quarters with a bristling, complicated question, beginning by being deceived about it, by seeing things the wrong side to, but led back continuously to the truth by experiment, and ending by unravelling all the obscurities. I do not know a more beautiful example of scientific investigation. The second reason is that it is the first camp on a route wherein he found immortality. The other discoveries had given him only glory. Finally, I would like to add, as a third reason, that this period of his life is that of which it is easiest to write the history, both because of the impressions it has left on those who helped him in his labors, and because of the documents he has himself published.

In this part of his researches he had not the right to keep the Olympian silence with which he loved to surround himself until the day in which his work seemed to him ripe for publicity. He said not a word about it, even

in the laboratory, where his assistants saw only the exterior and the skeleton of his experiments, without any of the life which animated them. Here, on the contrary, he was under obligation as soon as he had found out something to speak and to excite the public judgment and that of industrial practice on all his laboratory discoveries.

A hard necessity, that of laboring thus under the public eye, with an official connection, in the presence of a menacing danger which one has been commissioned to exorcise! To be sent to combat a conflagration, and not to know where the fire is, and not to have any pumps! One must be a Pasteur to accept such a responsibility and carry it off successfully. In any event, we owe to this condition of things a multiplicity of documents: reports to the Academy of Sciences, to the Minister of Agriculture, letters to M. Dumas, communications to the journals of silk culture, and we can make use of all these signed writings of Pasteur to reconstruct the history of his thought. He has himself authorized us to consult them by inserting them at the end of the second volume of his *Études sur la maladie des vers à soie*. "I might have dispensed with reproducing *in toto* these publications," he says, "since the first volume contains the definite expression of my actual ideas; but I have thought that they might be of some historical interest and serve as an example in a difficult and long-winded subject of the progressive march of ideas in proportion as the observer multiplies his experiments.

"Let us gather together some facts in order to have some ideas' said Buffon. It is not without utility to show to the man of the world or to the practical man at what cost science conquers principles the simplest and most modest in appearance."<sup>1</sup>

<sup>1</sup> *Étude sur la maladie des vers à soir*, t. II, p. 155.



We shall see that Pasteur has nothing to lose from this attentive study of the progress of his mind. He sometimes wandered in his research, as we have said, allowing himself to be deceived by false gleams, but he always returned to the right path, and it is just this struggle with error, always imminent, that makes the interest of this study.

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## II

### THE CORPUSCULAR DISEASE [PÉBRINE]

Some preliminary notions and details are necessary to understand thoroughly the moving vicissitudes of this struggle against a scourge as redoubtable as was the disease of silkworms at this time. Everybody knows, at least in a general way, the principal phenomena of the life of the silkworm: its birth from an egg, whose resemblance to certain vegetable seeds has led to its being given the name of *graine*; and its four *molts* or changes of skin, during which the worm ceases to eat, remains motionless, seems to *sleep* upon its litter [feeding place], and clothes itself, under its old skin, with a new supple and elastic skin, which allows to it a new development. The fourth of these *molts* is followed after two or three days by a period of extreme voracity during which the worm increases in volume rapidly and acquires its maximum size: it is the *big gorge*. This period terminated, the worm eats no more, moves about uneasily, and if sprigs of heather on which it can ascend are offered, it hastens to choose thereon a suitable place to spin its *cocoon*, a kind of silky prison which permits it to undergo in peace its transformation first into a chrysalis, and then into a moth. In this cocoon, the body of the worm, emptied of all the silky matter, contracts and covers

itself with a resistant tunic, in the interior of which all the tissues seem to fuse into a pulp of homogeneous appearance. It is in the midst of this magma that, little by little, the tissues of the moth are formed and become differentiated.

The moth has only a rudimentary digestive canal, for it no longer has any need of eating: the worm has eaten for it. It has wings, but, in our domestic races, it makes no use of them. It is destined only for the reproduction of the species, and the sex-union takes place as soon as it comes out of the cocoon. The female then lays a very considerable number of eggs, which may reach 600 or 800 and in the races that we call annual, which are the most sought after, this "graine" does not hatch the same year as its production. It is delayed till the reawakening of vegetation the spring of the following year.

It is only when the grower wishes to have "graine" or to induce the laying of eggs (*faire grainer*) that he awaits this coming forth from the cocoon, in which the transformation of the worm into a moth requires about 15 days. By adding thereto the 35 or 40 days required for the *culture* of the worm, and the time necessary for the laying of the eggs, we see that the complete evolution of the silkworm, from the egg around to the egg is about two months. The period of industrial life is sensibly shorter. When the grower wishes to use only the cocoons, he must not wait till the moth, in coming forth, has opened them and thereby rendered them unfit for spinning. They are *smothered* 5 or 6 days after they have climbed the heather twigs. That is to say, the cocoons are put into a vapor bath in which the chrysalids are killed by the heat. For the silk grower, in this case, scarcely six weeks separate the time of egg-hatching from the time when he carries his cocoons to market—

the time when he sows from the time when he reaps. As formerly the harvest was almost certain and quite lucrative, the *time of the silkworm* was a time of festival and of joy, in spite of the fatigues which it imposed, and in gratitude the mulberry tree had received the name of *arbor d'or* from the populations who lived upon it.

Unfortunately, silk culture had been attacked for 20 years by a cruel, inexplicable disease, which owing to its singular behavior and multiple and changing manifestations, disconcerted the reason and baffled the efforts best calculated, in appearance, to overcome it. If, for example, a culture of worms had succeeded very well so as to excite the admiration of all the surrounding country: instead of smothering it to wind the cocoons for silk, it was saved for the egg-laying in a very natural hope of obtaining therefrom excellent "graine." But alas! It happened that almost always this hope was deceived and that the following year the worms derived from these eggs, instead of growing rapidly like their ancestors, and preserving to the end a perfect uniformity, acquired slowly the most diverse sizes. Many died in the first stages, and those which had passed the fourth molt successfully seemed but little able to pass beyond it; they became smaller, seemed to melt away, little by little, and ended by disappearing almost altogether, giving only a negative or insignificant yield. The impossibility of obtaining good eggs which was soon demonstrated by similar failures with our fine French races, had led numerous silk growers to travel seeking healthier eggs at a distance; but the disease seemed to have made the tour of the world along with them, and their exotic "graines," after having succeeded one or two years in France, were struck with sterility both in our own country and in the lands where they originated.

On account of its occurrence in cultures which it ap-

peared should be the most robust, the disease seemed to be epidemic, and on account of its slow and regular progress, from our country toward the most distant regions of Europe and Asia, it seemed to present in the highest degree the contagious character: and yet other facts, not less numerous, and not less convincing in appearance, bore witness that it was neither epidemic nor contagious. I will cite only one of them, which Pasteur had learned at the beginning of his studies, and which had troubled him somewhat. In the culture of a mixture of two "graines," the one giving white cocoons and the other yellow ones, it had been observed that the first died almost completely, while the other gave a very satisfactory harvest.

The uncertainty was not less great if one sought to study the disease by itself, without being preoccupied any more with its nosological character. Thus, de Quatrefages, after having made a careful study, believed himself able to characterize it by the existence in the interior and especially upon the skin of the worm, of very small spots resembling grains of *black pepper*, and for this reason had been led to name it *pébrine*. But experiment showed that the worms could be spotted without being sick, and on the other hand that worms which were not spotted did not necessarily give good eggs. If one wished to enter further into the study of the disease, he found himself in the presence of contradictory results obtained by various physiologists. For example, Lebert and Frey had established that in the interior of all the diseased worms and all the diseased moths there existed in abundance a peculiar parasite, the corpuscle, visible only under the microscope, observed for the first time by Guérin-Mèneville, and the importance of which from the pathological point of view had been caught sight of by Cornalia. But if one believed Philippi, another

scientific man, these corpuscles existed normally in all the moths.

A real progress had, however, been realized the day that Osimo had discovered the corpuscles in the eggs of silkworms, and the day Vittadini, after having recognized that their number increased in a laying of eggs in proportion as they approached the period of hatching, had based a method of distinguishing the good from the bad upon a microscopic examination of the eggs. The corpuscle is, indeed, actually, as we shall see, the cause of the disease, and an egg which contains it can never give cocoons; but these two facts not being demonstrated, uncertainty existed as to the theoretic value of the procedure. As to the practice, it often gave out detestable eggs for good ones, and when it condemned the eggs it was in the name of principles so uncertain that the silk grower could not be held culpable for having no confidence in the advice of science.

The same Osimo, in 1859, had endeavored to push science and practice in another direction. He had advised examination not only of the eggs but also of the chrysalids, and rejection of the layings of those stocks which were found too corpuscular. This time it would have been to approximate correct procedure, as we shall see immediately, but this advice, given offhand, and without experimental support, had been followed and tested, offhand also, by Cantoni, who, after having cultivated the eggs coming from non-corpuscular moths, had seen the worms become corpuscular during the culture, which proved, he had concluded, that "the microscopic examination of moths was also unfortunately as worthless" as the other remedies.

By good fortune, of all this past history, of all this mixture of truth and falsehood, Pasteur knew nothing at the beginning of his studies. To his complaint of

not being familiar with the subject, Dumas had replied one day: "So much the better! For ideas, you will have only those which shall come to you as a result of your own observations!" Such a reply is not always a paradox, but one must be careful to whom he makes it.

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### III

#### STUDIES OF 1865

The first act of Pasteur on reaching the South was to seek this famous corpuscle, which he had never seen. He had no trouble in finding it. In the neighborhood of the little city of Alais, in which he had installed himself, all of the cultures, already near their end, were infected. Sick worms and moths showed the corpuscles by thousands. Some rare worms of healthy appearance did not show any. What seemed especially to result from this first rapid examination was the exactitude of the relation pointed out by de Quatrefages between the existence of the corpuscles and the presence on the surface of the skin of the black spots of the *pébrine*. All the worms having *pébrine* showed corpuscles in enormous numbers. But this fact, even though it might have been more thoroughly settled than it was really, did not signify very much. In continuing his researches, a little at random, Pasteur one day encountered one of those unexpected facts which it is so useful and so dangerous to find on our pathway, when we begin any research whatsoever. They have a sphinx-like physiognomy, and, in fact, they put the riddle clearly: "Guess or be devoured." Pasteur did not guess and was not devoured. Therein lies the interest of this history.

Near the silk nursery in which he had installed himself,

there were two cultures of silkworms, two *broods* (deux chambrées): the one finished and ascended to the heather, the other coming out of the fourth molt. The first had *gone along admirably*. The worms had climbed up all at one time, and appeared so vigorous that they were preparing to make use of all the cocoons for the egg-laying. The second had *dragged along*, and presented a bad appearance; the worms were languishing, ate little, and did not grow. The sequel proved that this appearance was not deceptive: the harvest of cocoons was almost a failure.

Now, on examining with the microscope the *chrysalids* and the *moths* of the culture which had *succeeded well*, corpuscles were found everywhere in them, while there were corpuscles only exceptionally in the *worms* of the bad brood. And this was not an exceptional fact, for, by searching in the neighborhood, Pasteur found a multiplicity of similar cases.

What did this mean? The corpuscles and the disease of silkworms were, therefore, two distinct things. Could worms be very healthy and behave properly, like the worms of the first culture, and nevertheless give corpuscular chrysalids? Could they be sick, like the worms of the second, and not contain corpuscles? To-day we know that if Pasteur did not find out this it was because he investigated badly, confounding in his inexperience two diseases. There is one in which the corpuscle plays a rôle, another in which it does not. But Pasteur did not know this, having only discovered it later. And, in the meantime, the disturbing and imperious question confronted him: what conclusion is to be drawn from the preceding observation?

In order to decide, it was prudent to wait and see what would become of the cocoons of the bad brood. In fact, in studying them day by day, as they developed, Pasteur

saw that the number of those containing corpuscles increased more and more. Among the worms, the corpuscles were rare. In the chrysalids, especially in the older ones, the corpuscles were frequent. Finally, not a single one of the moths was free from them, and they were there in profusion.

The question seemed, therefore, to be cleared up, for how could one interpret this double observation otherwise than by saying: there is a disease which can weaken the worm in the absence of the corpuscle, but of which the corpuscle is the tardy evidence. The two broods have suffered from this disease but the first has been attacked only when the worms were near the cocoon stage, and this brood has succeeded well although it has been a little diseased. In the second, the disease has attacked the worms more severely, and it is for this reason that this brood has been languishing and has almost miscarried.

This interpretation, we know to-day, is inexact, and, consequently, it was perilous. Its danger was that it led to a practical conclusion which Pasteur did not hesitate to draw. From the moment that the corpuscle appeared thus as the evidence of an advanced disease, it is clear that it would be more advantageous to obtain eggs from the non-corpuscular moths rather than from the corpuscular moths. The first might be diseased, but they would have been so for a shorter period and probably less seriously. "To say that the disease should be regarded as affecting by preference the chrysalid and the moth is only to say that at this age it manifests itself more apparently and also without doubt more dangerously for its posterity." It is thus that Pasteur, starting from a false idea, immediately put the capstone upon a method of egg-selection which became theoretically and practically, still better when the false idea which had



inspired it was replaced by a true idea. For the corpuscle becoming, as it is really, the sole cause and not simply the effect, or the witness, of the disease, its elimination was all the more profitable, and it is thus that error sometimes leads to the truth. But let us not trust too much to this example.

However this may be, Pasteur found himself led by his manner of seeing things, to the same method of egg-selection as Osimo, and it is curious to note with what firmness, after 15 days only of sojourn in the places, he indicates to the Agricultural Committee of Alais,<sup>1</sup> the 26th of June, 1865, and repeats the 25th of September following, before the Academy, the conditions of a good method of egg-selection. "This means will consist in isolating, at the moment of egg-laying, each couple, male and female. After the mating, the female, set apart, will lay her eggs; then one will open her, as well as the male, in order to search therein for the corpuscles. If they are absent both from male and female, he will number this laying which shall be preserved as eggs absolutely pure, and bred the following year with particular care. There will be eggs diseased in various degrees according to the greater or less abundance of the corpuscles in the male and female individuals which have furnished them."<sup>2</sup>

It is, on the whole, a return to the procedure of Osimo, tried and judged worthless by Cantoni, as we have just said. Why had it miscarried when it ought to have succeeded? Perhaps because it had not been tried with confidence, with the necessary faith, perhaps because Cantoni had not sufficiently protected his worms from a new contagion, the effects of which he had confounded with those of heredity. When one follows an idea *in*

<sup>1</sup> Études sur la maladie des vers à soie, t. II, p. 159.

<sup>2</sup> Comptes rendus de l'Académie des Sciences, t. LXI, 25 Sept. 1865.

*the air* he must indeed go haphazard, and the least check discourages. The idea of Pasteur had, on the contrary, an experimental foundation, and any one could trust him when he followed an idea proceeding from experiment. Ordinarily he distinguished very quickly whether a thing was true or false.

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## IV

## STUDIES OF 1866

However, in the subject under consideration, Pasteur continued to deceive himself during the whole of the year 1866, in consequence of a defect of technique which we must notice. He had had at heart to apply himself his method of egg-selection in order to procure materials for study the following year. He had, therefore, sought in the vicinity of Alais chrysalids and moths as healthy as possible. But the country was thoroughly infected; moreover, the cultures were far advanced in that place, and for the greater part had been used for the spinning. It was with great difficulty that he could procure a few cocoons derived from a culture in appearance quite healthy and successfully completed. He brought them to Paris to obtain their eggs.

In the passage which I have just transcribed, Pasteur says that one *opens* the male and female to seek therein the corpuscles. They proceeded at that time by removing with scissors a part of the skin of the abdomen: they spread out this shred upon a glass slide, scraped off a little of the adipose cellular tissue which was brought away with it, and examined this fragment after having compressed it under a cover-glass. It was only later that the moth was ground up in a mortar to study a drop of the pap under the microscope. This slight

detail has a very great significance. The second process is the only reasonably safe one.

On the contrary, the first method is liable frequently to overlook the presence of the corpuscles, and we shall see here how things go on in a research. The method then adopted by Pasteur was the result of his false idea. If Pasteur had considered these corpuscles as parasites, he surely would have concluded that they might be in one place and not in another, and that it would be necessary to seek them in various places. But he was convinced that the corpuscle, being a tardy sign of the pre-existing disease, was a product of transformation, or, to employ a medical expression, a product of retrogression of the cells of the tissues. Now, following this hypothesis, it should occur everywhere in the body.

The method of research, imperfect because it had been born of a false idea, deceived Pasteur and plunged him deeper into his idea. In the eight couples brought from Alais and which he had studied in Paris, he believed he had found one in which the male presented a few corpuscles, and the female not any. As a matter of fact, she also contained them, as shown by the result of the cultures in which a few corpuscles appeared, not in the worms and the chrysalids coming from these eggs but in the moths. This phenomenon, spontaneous in appearance, of corpuscles in a culture which it seemed ought to be exempt, naturally confirmed Pasteur in his belief in the internal origin of the corpuscle. It is thus that a mode of examination inspired by a false idea leads sometimes to the confirmation of this false idea, and it is thus moreover that, during the whole of the campaign of 1866, Pasteur persisted in likening the corpuscle to pus-globules and even to red blood-globules. He came back definitely to the idea of parasitism only after an experiment of Gernez which we shall find in its place.

On the whole, at this time, any one who judged superficially would have concluded that Pasteur brought forward nothing new. He shared the error of Philippi, of Vittadini, and of Cornalia, upon the origin of the corpuscle: his method of egg-selection, proposed by Osimo, and then by Cornalia, had miscarried in the hands of Cantoni and of Bellotti. It is necessary to look at the subject closely to see that Pasteur brought into this study another idea than his predecessors. This idea was that of undertaking comparative cultural experiments upon healthy eggs and diseased eggs. The method of egg-selection which he recommended, however mediocre it might be from the theoretical point of view, however bad it might be from the industrial point of view, judging from the results of Cantoni, was, however, sufficient to maintain those original differences between the eggs, the influence of which it was important to examine. "The process of selection to which my first researches had led me seemed to me," says Pasteur,<sup>1</sup> "to have an importance more scientific than industrial." It turned out that this process contained the industrial solution of the problem, but if it had not contained it, it would have led to it, for Pasteur introduced experiment into a question where there had been hitherto only empiricism.

His plan of campaign for the cultures of 1866 was, therefore, already outlined. After having obtained the eggs from his different pairs of moths which were more or less corpuscular, he would first try these out ahead of the main brood, which is done in March and April in small lots upon leaves of the mulberry cultivated in hothouses, then in the big cultures of May and June. Made with the same precautions and under the same conditions, the culture of these eggs of different origin

<sup>1</sup> *Études sur la maladie des vers à soie*, t. I, p. 55.

ought to give, as regards the influence of the corpuscles of the father and of the mother upon the result of the industrial culture, or of the culture for eggs, information which could not fail to be very important, whatever might be the true significance of the corpuscle itself. In fact, advancing with this light, Pasteur perceived immediately a certain number of facts of the greatest importance.

The first fact was that on a large scale in the industrial culture the batches of eggs behaved worse and worse, that is gave less and less cocoons, in proportion as the parents were more and more occupied by corpuscles. This sufficed to establish between the existence or the number of the corpuscles and the presence of the disease, the bond of union which was the first need of the new method.

The second fact was that eggs laid by corpuscular moths were not, *per se*, destined to miscarry, and might develop good cocoons giving acceptable yields. Such was, for example, the case of the eggs received from Japan, which, although corpuscular, were nevertheless much sought after by silk-growers. This robust race seemed better to resist the prevalent disease. Such was also the case for several cultures of French races. But none of these cultures, even those which had yielded the greatest number of cocoons, could give good eggs, because all the moths were strongly corpuscular. This explained why one sometimes miscarried in selecting eggs derived from a successful culture. The success of this culture proved nothing as to the egg. In addition, control by means of the microscope was necessary. And so one came back to the method of egg-selection, authoritatively recommended by Pasteur, this being brought forward once more, singularly strengthened by its first trial.

Finally, another prime fact was that even in the most corpuscular broods, where the mortality of the worms or of the chrysalids had been the greatest, one always found some non-corpuscular moths that would give better eggs than those from which they themselves had come. From a practical standpoint this was of the highest importance. Among the objections made to Pasteur, from the beginning, the following had actually figured: If the disease is indeed characterized by the presence of an abundance of the corpuscles, as you say it is, and as you prove it to be, it is then widespread, universal, and, this being so, how shall we proceed to find the necessary eggs, we do not say for the regeneration, but for the simple conservation of the French and Italian races, very superior from the point of view of yield and of the quality of the silk to the Japanese races, which are replacing them little by little in all the silk-growing lands. To this Pasteur could reply: But here are cocoons of a French race which I have just brought from one of the most infected districts! Look at them, study them under the microscope, and you will see that they promise results still more beautiful for next year. Do, therefore, as I do: let each one procure eggs for himself, as I do for myself. If you tell me that the microscope frightens you, and that its manipulation seems to you not easy, I reply that there is in my laboratory a little girl eight years old who knows how to do it very well.

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## V

## IS THE CORPUSCLE THE CAUSE OF THE DISEASE?

But this apparent disappearance of corpuscles in some of the moths descended from a corpuscular pair had theoretical consequences more far-reaching than its practical

consequences. What signified these healthy individuals in a progeny strongly infected from both parents, and evidently attacked by a hereditary taint? "Can it be that among the eggs of a laying, derived from a male and a female badly diseased, there are some healthy eggs? Or will some eggs slightly diseased give worms which recover health during the culture? I do not know which of these two interpretations is the better, and both are perhaps correct."<sup>1</sup> The phrase is curious, and bears witness that Pasteur began to doubt in 1866 concerning the interpretation of the phenomena which he had accepted hitherto. The idea of a constitutional disease of which corpuscles were only the external and later sign did not harmonize very well with this presence of a few healthy eggs in the midst of their diseased neighbors. Excluding parasitism, one does not comprehend this immunity of some individuals in the midst of others entirely alike in that they are the descendants of the same organism. But this idea of parasitism, which was blended with the idea of the corpuscle as a cause of the disease, was repulsed by Pasteur at this moment with a kind of obstinacy, and with such a singular mixture of true and false arguments that it is useful to pass them in review. To do so will be to study him in a vital point of his career, that in which he abandons tradition and launches out into new ways.

He enumerated these arguments himself the following year, for his scruples were of long duration. "Is the disease parasitical?"<sup>2</sup> he asks himself in the note presented to the *Imperial Commission of Silk Culture*, in its sitting of January 12, 1867, and he rejects this opinion for the following reasons:

1. "Because the disease is certainly constitutional in

<sup>1</sup> *Études sur la maladie des vers à soie*, t. II, p. 165.

<sup>2</sup> *Études sur la maladie des vers à soie*, t. II, p. 181.

a great number of circumstances, and precedes the appearance of the corpuscles." We recognize there the influence already noted by us of that preliminary observation on a culture which behaved badly although the worms did not contain corpuscles. We know to-day that Pasteur had fallen by chance upon a culture attacked by another disease than pébrine, the disease of *morts-flats*.<sup>1</sup> Pasteur, who, at this moment, spoke only of *the* disease of silkworms, had confounded everything and could believe in a disease of corpuscles without corpuscles;

2. "Because the feeding of corpuscular substances often kills the worms without giving them corpuscles." Here again, there was an error of interpretation, due to the same reasons as the above. Pasteur had very clearly perceived that the *criterion* of the corpuscle as cause, and of the corpuscle as effect and evidence of the disease, was an inoculation experiment. If it had been possible to give the corpuscular disease to healthy worms by causing them to feed upon corpuscles derived from a preceding silkworm culture, one would have singularly enlightened not only the etiology of the disease, but also the causes of its vitality and of its propagation, of its endemic and epidemic character. With Pasteur the execution followed close upon the idea, and the experiment was made. He had taken, in 1866, as infectious matter, very corpuscular dirt scraped up in a culture chamber, and the mashed substance of a very corpuscular moth or worm. The worms to which he had fed the leaves of the mulberry, thus infected, had showed at the end of some days a considerable mortality which Pasteur had the right to attribute to the infected food and to the prevailing disease: in reality it again resulted from the intervention of the disease of the *morts-flats*. But

<sup>1</sup> Flacherie. *Trs.*



seeing worms inoculated with corpuscular materials die rapidly and yet not contain corpuscles, we still understand how Pasteur may have been able to believe that the corpuscles not only were not the cause of the disease, but were not even the constant sign of the disease, and could be absent when the disease was in too rapid evolution, for example, when the substance relied upon to produce it had too active toxic qualities and killed the worm too quickly, as was apparently the case in these two experiments;

3. "I have not been able," continues Pasteur, "to discover up to the present time a mode of reproduction of the corpuscle, and its manner of appearance makes it resemble a product of the transformation of the tissues." Here Pasteur paid the penalty of his inexperience in the world of beings to which the corpuscle belongs, a world where the forms of reproduction are quite other than in the world of microbes, which he knew the best. Without entering into details, we must know that the corpuscle, instead of increasing by segmentation or by budding as do the bacilli or the yeasts, can, under certain circumstances, swell up into a voluminous protoplasmic mass with almost invisible contours. This insinuates itself into the tissues, penetrates them with an almost invisible network in which then only begins the process of delimitation which divides it into distinct and sharply contoured corpuscles. From the initial corpuscle we have come to some thousands of identical corpuscles, children of the same father. Pasteur had indeed seen this phenomenon of the organization of a sort of amorphous matrix. He described it with a marvelous precision because he was a master observer. He pointed it out to his draftsman, Lackerbauer, who strove to represent it in two plates (pp. 28 and 64). But he does not know how to interpret it, and, as he sees

the corpuscle appear in the midst of all the tissues of the diseased worm, he is confirmed naturally in his idea that the disease is constitutional and that the corpuscle indicates only one of the stages of it, that in which it becomes apparent under the microscope.

It is a singular thing, that while his spirit marched in these pathways and would not be turned aside, his assistants (*préparateurs*), to whom he said nothing of what he thought, were persuaded that he was firmly attached to the idea of the corpuscle as a cause. They were astonished that he did not make the crucial experiment, and endeavor to give to healthy worms by means of corpuscular food, not the disease with a rapid evolution of which we have just spoken and which did not resemble the corpuscular disease, but that same disease with its slow evolution and concomitant development of the parasites. Relying on the interpretation he had given to his first experiment, Pasteur did not hasten to begin a second. When that appeared useful to him it was too late. He was in Paris. His associate, M. Pélignot, could, nevertheless, give him some worms of a culture which was delayed. With these the inoculation gave results quite other than at Alais; the worms had not, apparently, suffered from the contaminated food, and Pasteur was very much embarrassed until he learned that Gernez had at Valenciennes semi-annual Japanese "graine," that is to say, eggs which would hatch the same year they were laid, and give a second culture of worms. Moreover, these eggs were healthy, the parents not being corpuscular. He, therefore, asked Gernez to do over the experiment which had been made at Alais with worms obtained from Pélignot, and observe whether the difference in results obtained in Gard and in Paris was not related to the age at which the worms had been subjected to the contagion of the disease. For him it was always the

question of seeking the relation which existed between the time of the corpuscular feeding and the development of the disease with or without corpuscles. For Gernez, who believed Pasteur converted to the idea of the corpuscle as cause, the question was simpler: the only question was to know whether the inoculated worms would have corpuscles, and the healthy worms would not have them. From this point of view, his experiment was particularly convincing. Of four lots of 40 worms each:

The first, fed with ordinary leaves, gave 27 healthy cocoons;

The second, fed with leaves moistened with ordinary water, gave 19 cocoons of which not one was corpuscular;

The third, fed after the third molting with leaves moistened with water containing the débris of corpuscular moths, gave only four cocoons which were very corpuscular.

The fourth lot, in which the feeding of corpuscular leaves had commenced only after the fourth molt, gave 22 cocoons, all or almost all corpuscular.

Here we behold a spectacle rare in the life of Pasteur: an experiment the full and complete meaning of which he does not immediately comprehend. This experiment was highly pertinent. It realized as in a synthesis the principal aspects of the disease. The third lot was an example of those silkworm cultures which, after having begun well, perish by the way and do not reach the cocoon stage. The fourth lot was an example of those cultures which succeed well but are incapable of furnishing good eggs. The first and the second lot bore witness to the worth, when it is not infected, of a "graine" resulting from egg-selection under the microscope, made upon a diseased culture. All that spoke at the same time in favor of Pasteur's method and of the corpuscle as a cause, but Gernez, who believed his master converted

to this doctrine, was somewhat astonished that Pasteur saw in his experiment only the practical side and did not flash everywhere the light which shone out of it. In reality, Pasteur had not seen it. The proof is that this experiment was announced to the Academy by him the 26th day of November, 1866, and that in January, 1867, he was still asking himself whether the disease was parasitic, and was still advancing against this idea the arguments which we have just examined. He changed his opinion on this subject only during the course of the year 1867, and this change of front has made that the decisive year. He had until then marched directly toward the promised land, but he had marched backwards. As soon as he turned about, the whole of his conquest appeared to him at once.

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## VI

### STUDIES OF 1867

He began in fact the early experiments of 1867 with clarified ideas, and also, which was not less important, with means for work and experiment. The eggs which he had prepared in 1865 and which had served for his experiments of 1866 were not, as we have seen, wholly freed from corpuscles. By raising them under special conditions of cleanliness, by giving to his worms space so that they would not infect each other, by isolating the divers lots in separate baskets, by shiftings, that is to say by removing the broods into the open air, all practices which, in his mind, were so many hygienic measures as well as precautions against contagion, he had succeeded in having in 1866 a great number at least, if not whole lots, of moths which were non-corpuscular,

giving with certainty eggs that Pasteur was content to call healthy, but which to-day we would say were free from parasites. It was with these eggs, the hereditary conditions of which he knew, that he began the tentative experiments and the large cultures of 1867.

The first thing which he had to ask himself, since he had not yet renounced the idea of a constitutional disease existing before the appearance of the corpuscles, was whether the districts of silk husbandry truly constituted, as was said over and over, a deleterious center, an infected district, in which the disease and the corpuscle would appear inevitably, carried by the ambient air into the healthiest broods. This doctrine spoke too much in favor of inaction and indolence, not to have many partisans.

To this objection Pasteur was able to respond at the end of his preliminary experiments by showing some lots of worms, offspring of non-corpuscular parents that had passed through the entire metamorphosis without being attacked, and had produced eggs which in turn were free from corpuscles, and this too, although they were raised not only in an infected district, but in a silkworm nursery where by the side of them, other lots died from the disease. Not only did the sound worms remain sound, but their general health seemed to be improved, and from 1865 to 1866, from 1866 to 1867, one saw the broods improve just in proportion to the original purity of the eggs.

Assured now of not seeing the corpuscles appear in these sound lots, one could perform experiments on corpuscular contagion, beginning it at different ages, could repeat on a large scale the experiment of Gernez, and could synthesize the results. This synthesis is most clear, and we may summarize it very simply.

If we take sound worms and make them swallow or

by puncture inoculate them with fresh corpuscles taken either from a diseased worm, or from its excretions, the worms thus treated are sure to be attacked with a disease which, in its external characters, recalls completely pébrine, and correlatively, the corpuscles thus introduced into their organism, develop there until they have invaded it throughout. The corpuscle is, therefore, the cause of the disease, and pébrine is due, and due solely, to the abnormal development of these little organisms. All uncertainty has disappeared, and Pasteur adopts anew the doctrine of the corpuscle as cause, and the parasitic theory.

Fortunately, the progress of the disease is not as rapid as it is certain. It is nearly 30 days after infection before the animal is sufficiently invaded by the parasite to be truly sick, and to be able no longer, for example, to spin its cocoon. As its life in the larval state is only about 35 days long, every worm which comes from a sound egg, that is to say which does not contain at the moment of its birth corpuscles in process of development, will almost surely produce its cocoon. In order that it should be otherwise the larva must become diseased in the first days of its existence, at a time when the malady is still, so to speak, latent in its neighbors, even in the most infected ones, and when there are a thousand chances that it will not come into contact with any mature corpuscles which it could swallow or with which it could be infected through wounds. Therefore, if an egg is sound, that is to say, free from corpuscles, the offspring cannot die from pébrine. Here evidently we have a fact of capital importance, and it is not the only one of this order.

There results, in reality, from this long period of incubation of the disease, another consequence: that is that the silkworm, passing from 15 to 20 days in its

cocoon, if it is ever so little diseased at the beginning of this period, and it may be so slightly as to appear perfectly sound even under the microscope, becomes more and more diseased, the few corpuscles which it contains multiplying little by little within it. They invade all the tissues of the chrysalis and especially those in the midst of which the eggs are formed. Consequently, the latter may include some of these corpuscles in their interior, and the worms which are hatched from them, corpuscular from their birth, cannot as we have seen, reach the cocoon stage. The grower will obtain then a commercial harvest from an egg only when it is pure, and there is no certainty of its being pure unless it comes from moths free from corpuscles.

We are, therefore, now authorized to say that the disease is contagious and hereditary, but we must give to these two words, *heredity* and *contagion*, a well-defined sense, for they both represent the introduction, either into a sound worm from its diseased neighbors, or into an egg from a corpuscular female, of one sole element, the corpuscle in process of development. Pasteur has even gone farther, and by showing that at the beginning of a silkworm season there are no living corpuscles except those which are contained in diseased eggs he has connected these two questions of contagion and heredity. All other corpuscles, all, for example, which are present in such great abundance in the dust of the hatcheries, are dead and incapable of reproduction. It is, therefore, the hereditary corpuscles alone which permit the malady to assume each year its contagious character, and it will disappear forever on the day when, throughout the entire world, silkgrowers raise only sound eggs.

Such are the theoretical conclusions of the experiments of 1867. The practical conclusions are not less clear cut. "Do you wish to know," said Pasteur to the

silk-growers, "whether a lot of cocoons will give you sound eggs? Take a portion of them and heat them so as to hasten four or five days the hatching of the moths, and see whether the latter are corpuscular. The microscopical examination of the moths is easier and more certain than that of the eggs because in them the corpuscles are many times more abundant. If the moths are bad, send the cocoons to the spinning mills. On the contrary, if you find that only a very limited number of individuals are diseased, allow them to develop: the eggs will be good and the brood which you will have from them the next year will be a successful one. Only, this brood will be unfit for breeding because of the initial presence and multiplication in it of the corpuscles. But do you wish the brood to be sound up to the very end and give you perfect eggs? Then take absolutely sound eggs, coming from absolutely pure parents, and hatch them in conditions of cleanliness and isolation, such that infection cannot spread there. But if, unfortunately, the disease should appear I still give you the means of making a selection, and of separating rigorously the sound eggs from the corpuscular ones."

The problem was, therefore, solved, and the victory could be considered complete. Let us hasten to say that no part of it is more widely discussed at the present time. The examination of eggs with the aid of the microscope which had been judged impossible has become a custom. The growers of silkworms have made it encircle the globe as they once did the disease itself, and pébrine has ceased to haunt the mind of those engaged in the silkworm industry. On one point only were the expectations of Pasteur unfulfilled. He hoped that it would be possible to make the disease disappear. This was a noble ambition and would have been a great example. Experience has shown that it was impossible. This is



because the silkworm is not the sole host of the corpuscle, and do what you will to make this source of contagion disappear, there are others open. In vain M. Susani, for example, eliminated for many kilometers around his immense establishment of Rancate in the Brianza every corpuscular egg: he still had corpuscular moths, and he was obliged all his life to defend himself every year against the contagion of the disease which he had tried in vain to extirpate. Man cannot suppress an epidemic disease, but he can keep it within bounds, and render it almost inoffensive. A great lesson, which, from the silkworm industry, has passed into pathology, and which we shall recall later when we see Pasteur grappling with human diseases!

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## VII

### THE DISEASE OF THE MORTS-FLATS [FLACHERIE]<sup>1</sup>

In what precedes, I have left out of consideration all the propaganda which Pasteur undertook in order to inspire and hasten confidence in his methods: visits, correspondence, letters to the journals, he neglected nothing; he distributed healthy eggs and diseased eggs, sought public judgments on the results of the silkworm cultures, prognosticated them so as to attract attention and stir up curiosity, and every morning there was a great mass of letters which he opened with emotion, smiling at the good news, attentive to the bad.

In 1867, Pasteur had distributed in small lots his healthy eggs prepared in 1866, and the success, we knew, had been general. However, as the letters came in announcing the result of the cultures, we found our

<sup>1</sup> There are no English equivalents. Both words refer to the gaseous condition of the feces, and mean death or disease due to flatulence. *Trs.*

master more and more anxious. He kept us so remote from his thought that we could not explain his uneasiness till that day when he appeared before us almost in tears, and, dropping discouraged into a chair said: "Nothing is accomplished; there are two diseases!"

He had in mind this disease of the *morts-flats*, concerning which I have already made brief mention. He had known it for a long time, indeed since his first sojourn in the South in 1865, where one of the two cultures of silkworms which served for the beginning of his deductions was attacked by this disease at the same time as by that of the corpuscles. But the cases of association were so frequent, precisely because the disease of the corpuscles was widespread, that Pasteur had considered the two affections as intimately connected and likely to disappear together.

During the silkworm cultures of 1866, the two diseases were somewhat separated both in fact and in his mind. He had sometimes seen the second appear in cultures hereditarily exempt from the first, and he had asked himself whether they were not independent. His publications at this time bear the trace of these preoccupations, which had not yet become a source of uneasiness. The cases of *morts-flats* had been rare, and had besides appeared here and there, without visible preference, like cultural accidents attributable to the growers.

It was in 1867, in the preliminary trials, and especially in the large cultures, that the gravity of the danger first appeared. Almost entire lots of eggs free from corpuscles and bred by various growers had perished everywhere of the disease known as *morts-flats*, whatever might be the circumstances of place, time, climate and culture. It could not be any longer a question of accidents: it was the manifestation of an inherited disposition, and on seeing these mishaps renewed, on finding

behind the disease which he thought he had conquered, another redoubtable disease, and one about which he as yet knew nothing, we can understand why Pasteur experienced and exhibited a moment of despair. The public, to which one shows only the finished work, is ignorant of the painful hours with which the scientific man, the artist, or the writer has paid in advance for the joy of his success.

Naturally, we strove as best we could to comfort the discouraged master. Since all was not finished, it was not necessary to conclude that nothing was accomplished, but only to begin over again if necessary. We were young and we had confidence, not in ourselves, but in him. Well employed were those hours in which we saw him struggling with these difficult questions, ceaselessly on the hunt, sometimes deceived in his previsions and hesitating, sometimes triumphant and marching with great strides. We did not always know whither he was bent, for he said little; but we tried to guess, judging from the circumstances, and rectifying our ideas by what we were allowed to perceive of his own.

This differentiation between the two diseases, which had now become evident, was a first step, and one of the most important, in the study of the second disease. Henceforth only what belonged to each disease need be credited to it. At the beginning of his researches, as we have seen, Pasteur had credited to the corpuscular disease results due to the other disease. Now, the light having penetrated into obscure corners, many difficulties and apparent contradictions were explained and even by going over recollections and records of experiments, and removing therefrom all that related to the disease of the morts-flats, a very considerable volume of data bearing upon it, was obtained.

The most striking feature in its history was its mani-

festly hereditary character. As we have said, it ravaged certain lots of eggs, which were sometimes distributed among a number of silk-growers, and bred, owing to this fact, under the most varied conditions, and which, nevertheless, were attacked at the same period, in the same age of the worm, as if they had all brought with them a germ of destruction. Most frequently after the fourth molt, during the period of voracity called the "big gorge," when the healthy worms greedily devour the foliage given them, the diseased worms were seen to be indifferent to the provender, crawling over the leaf without attacking it, even avoiding it, and having the appearance of seeking a tranquil corner in which to die. When dead, the worm sometimes softened and rotted, but sometimes remained firm and hard, so that one must touch it to be certain it was dead. At other times, when the disease attacked the worm more slowly, it climbed the heather, but with difficulty, slowly spun its cocoon, sometimes did not finish it but left it in the condition of *skin*, and died without changing into a chrysalis or a moth.

In recalling the conditions under which the production of the eggs showing this hereditary predisposition to the disease of the morts-flats had taken place, Pasteur remembered suddenly that one of the cultures had not been entirely satisfactory at the time the worms climbed up to undergo their transformation. The worms had climbed up *soft*, had *dragged themselves* at this time. Here Pasteur reaped the advantage of that constant and penetrating supervision which he exercised over everything. In a year, he had become an excellent breeder of silkworms. If he observed well, he knew also how to draw conclusions, and immediately he reflected that the eggs subject to this hereditary sensitiveness to the morts-flats must have come from those apparently successful

cultures, which he had used for the production of eggs because the worms did not contain corpuscles, but which showed, on climbing up the heather for their transformation, that peculiar sluggishness which he had sometimes observed. As in the corpuscular disease, the malady had not killed the progenitors, but was not the less menacing to their descendants.

Forgetting his discouragement, he set to work immediately upon this idea. There were still in the neighborhood some silkworm cultures attacked by the disease of the morts-flats. He took the cocoons they had yielded, satisfied himself of the absence of corpuscles, and obtained eggs from them. These eggs were used for the preliminary cultures of the following year, and as early as the 20th of March, 1868, he was able to announce to Dumas that, out of the seven lots thus selected from seven distinct cultures, six had miscarried at various ages, especially in the fourth molt, with the disease of the morts-flats.

“Consequently, there is no more doubt,” he added,<sup>1</sup> “that the disease of the morts-flats can be hereditary and attack a brood, independently of all conditions as to mode of hatching of the eggs, ventilation of the brood, excessive heat or cold to which the worms are exposed, conditions which without doubt may occasionally provoke this same disease. Hence, the imperious necessity of never using for the egg-laying, whatever may be the external appearance or the results of the microscopic examination of the moths, broods which have shown from the fourth molt to the cocoon, any languishing worms, or which have experienced a noticeable mortality at this period of the culture, due to the disease of the morts-flats. I insist again on this advice, and with more force than last year.”

<sup>1</sup> *Études sur la maladie des vers à soie*, t. II, p. 232.

He felt, however, that this prescription was a little uncertain. What is a languishing worm? One must be a good grower of silkworms to see it, and there were no longer any such. Several years of successive disasters had overthrown practices, experiences, and traditions. He must find for the disease a more palpable sign, and, for that purpose, must study it in its origins, in its etiology.

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### VIII

#### STUDIES OF 1868, 1869, 1870

The etiology of this disease was the work of the years 1868, 1869 and 1870, an intermittent labor, interrupted as it was by other occupations. The recommendation Pasteur had made to eliminate from the egg-laying everything that had the appearance of *flacherie* suppressed for the time being all grave fears on the subject of this disease, leaving the corpuscular disease alone in the foreground. It was urgent to prove to all the worth and the eminently practical character of the new method of silkworm breeding.

In this work Pasteur showed qualities not among those of which I have undertaken the history, because they do not form a part of his greatness, and because he could well have done without them. But I must mention them because they complete his physiognomy. These were the masterful qualities of a chief of industry who watches everything, lets no detail escape him, wishes to know everything, to have a hand in everything, and who, at the same time, puts himself in personal relation with all his clientele, asking both those who are content and those who are not the reasons for their opinions.

He knew well that a process of silkworm breeding which clashed with interests, which transformed commercial or industrial practices, could not make its way without arousing anger, without stirring up criticisms, the more bitter because they were not disinterested. He showed himself less and less sensitive to these attacks the surer he became of his facts, and no contradiction, even though it came from the *Silk Commission* of Lyons ever stirred him as much as those which he was obliged to encounter later in connection with his studies on fermentation or researches on anthrax and human rabies. Yet, as the diffusion of the method had become a practical question, he did not disdain to become a silkworm breeder, and he went voluntarily to preside at the installation of his process in the nurseries of the growers in the lower Alps or the Eastern Pyrenees, who invoked his aid.

It was in the intervals of this practical apostolate that he returned to his investigations on the malady of the *morts-flats*, which, as he studied it, showed itself to be more complicated than the corpuscular disease and more nearly related to human diseases. This relation was at the time still very vague in the mind of Pasteur, who had not studied medicine, and who had, furthermore, the faculty almost necessary, it seems, to men of his temper, of isolating themselves in what they do, and of working so much the better the less they look out of the window. But as these studies of Pasteur had brought him into the domain of pathology, had led him to examine a host of new problems, and had had clearly a reflex action on his later discoveries, perhaps it is well to state the point which he had reached in 1878, after 10 years of study, which was intermittent and interrupted by other pieces of work. It was just before, or at the beginning of his researches on anthrax, and the

subject had not ceased to haunt his mind. In this year, 1878, there was held in Paris a Congress on silk husbandry, where the subject of *flacherie* was much discussed, and where Pasteur often found himself moved to speak. From his discourses and conversations we gather the following resumé of his ideas on a question to which he never again returned.

We have described the external signs of the disease and we know also that the mortality may be considerable within a few days, which gives it a distinctly epidemic character. One might call it the *cholera* or the *typhoid* of the silkworm. But these are only words; let us endeavor to get at the facts, and at the causes.

The simplest examination shows that, as in the case of typhoid or of cholera, it is the digestive organs which are diseased. Sometimes their contents are all foamy, and in full process of fermentation. Sometimes, on the contrary, the fecal substances are in compact masses, hard, and of the same aspect from one end to the other of the intestinal tract, which seems to have become an inert receptacle. In all cases there is nothing resembling regular, normal digestion, the solid product of which is molded and separated into bits by the muscles of the anus, with the regularity of a machine for making Italian pastes.

On examining microscopically these normal excrements, we find therein débris of leaves but no microbes, or almost none. There is not, so to speak, any place for them in the powerful mechanism of the nutritive system in this animal, which seems made only to eat. It is quite otherwise in the diseased worms. Their digestive tract is full of microbes; these are bacilli, more or less plump, some of them spore-bearing, and micrococci in pairs and in chains.

This being the state of affairs, the question arises at



once: Is the disease contagious? Can it be carried from a diseased worm to a sound worm, its neighbor? It happens exactly in this disease that the excrements are ordinarily viscid and smear the leaves which the worms eat in common. If we imitate this natural contagion by making worms eat leaves smeared with the excrement of a diseased worm, we shall see them become sick in their turn, as in the case of the corpuscular disease. The *flacherie* is therefore contagious, like the *pébrine*.

But here is a difference: all the worms which had eaten the fresh corpuscles became sick at nearly the same time. The ingested corpuscle undergoes a regular evolution, and it is not in the digestive tract that it develops. It is not the same with the *flacherie*. Its stronghold is in the intestine, and the time which separates the moment of contagion from that of death may vary from 12 hours to 3 weeks, and even more, for invariably some of the worms escape death. Therefore, worms which resemble each other in regard to the corpuscle, no longer do so when exposed to the germs of *flacherie*. Thus it is that Pasteur encountered for the first time this question, then so new, of *receptivity* to germs, differing in different individuals of the same species.

He discovered a second question just as new to him, although it was a little less so to science, when he sought to learn whether the germs of *flacherie* from different sources were equivalent from the point of view of the production of the disease. Some bacilli taken from an artificial fermentation of mulberry leaves, for example, caused death in from 8 to 15 days. If we inoculate fresh worms with the substance taken from the digestive tract of the former, death follows in from 6 to 8 days. The virus is, therefore, augmented in intensity as the result of its passage through the organism.

Finally, the influence of the port of entry, which

Davaine was at this moment occupied in studying in anthrax, was also apparent to Pasteur through the comparison which he had made of the results of inoculation by pricks and by contamination of the digestive tract. We see what an excellent preparation these studies on *flacherie* gave him, and with what good reason he advised young medical students, who later learned the path to his laboratory, to read these two volumes on the disease of silkworms: the great teachings of microbial pathology are already found there.

This is not all. We have seen that the germ of the corpuscle is not common, and must be acquired from a living worm, or from one just dead, in order to preserve its vitality. Pasteur even believed, as we have seen, that it had no other habitat than the silkworm, and that man could make pébrine disappear by making the production of sound eggs universal. On the contrary, the appearance of *flacherie* is sometimes spontaneous, and my result from an accident or from some error during the breeding. Whence, then, come the germs? The germ is common, replies Pasteur. It suffices to leave in a flask, at summer temperature, a bit of bruised mulberry-leaf, in order to see appear in the maceration microscopic organisms in every way similar to those which one encounters in the digestive tract of the flatulent worms, a canal which, in fact, seems to have become an inert receptacle. In a healthy worm the tract arrests or prevents all development of microbes; in a flatulent worm, it opens the way for the germs which the leaf introduces, and, with approximately the same virulence, the germs of the flasks and the germs of the intestinal tract behave the same. That explains to us how the disease can appear sometimes without having been introduced from a distance, a thing which did not happen, at least so Pasteur thought, in the corpuscular disease.

The discovery of the common character of the germs of *flacherie* obliges us now to turn back and ask ourselves a question. Why, if this germ is everywhere, does it not develop always and everywhere? This is clearly a general question, like those which precede, and may be asked regarding a multitude of human diseases. The germ of tuberculosis is widely disseminated, we could say to-day. There is not one of us who has not inhaled it. We are exposed to it every day and everywhere! Why are not all of us tuberculous? To this question, not yet solved, Pasteur had made, concerning *flacherie*, a double response.

This intermittent and localized development of germs universally distributed can take place, he said, whenever external conditions, of which the grower is not always the master, favor the multiplication of the microbes, or enfeeble the digestive power of the worm. The animal is constantly taking in, with the leaves which it eats, germs which would develop in a flask and which do not develop in its digestive tract, arrested as they are by physiological influences. But imagine that they are more numerous for some reason, that the leaf is heated by fermentation before being served to the worm; or again that the number of germs remains the same, but that the worms have been weakened by a stormy period or by a stifling heat when no air is in circulation, or by the fact that the worm-nursery is too warm or poorly ventilated, or by the result of some other accident, and then the germs take advantage of the lowered resistance to multiply and the malady breaks out!

Finally, to this idea add the fact that the weakening of the digestive tract may be constitutional, organic, may result from the fact that the worms which were the larval ancestors of these eggs, were themselves sick at the time of their pupation or before, with the disease of

the *morts-flats*, and we have united by a common bond all the modes of appearance of the disease, both that which is encountered in the sporadic state on sound eggs exempt from all hereditary predisposition, and that which rages among the descendants of a brood where the *morts-flats* has been.

The disease of the *morts-flats* is then, like that of the corpuscles, a contagious disease, but sometimes because its germ is so common, it *may* become a disease which appears to be spontaneous, sporadic or epidemic, benign or disastrous, and the origin of which a superficial observer might, with reason, attribute to the common conditions of cold, heat, humidity, electricity, so often invoked by ancient medicine. More enlightened now, we can say: No, these common influences neither are the disease nor make the disease; they open the door for it and give it scope. In this case, and in all the cases where one is led to lay on them the blame, we find on close investigation a germ, more or less widespread, ordinarily kept within bounds by natural laws, but able when conditions change, when its virulence is exalted, when its host is enfeebled, to invade the territory which was barred to it up to that time. The bacillus of *flacherie* is always present, but the sound worm is able to defend itself on the side where it is threatened. It will not, perhaps, resist a wound—an unusual way for contagion; it will better resist an introduction into the digestive tract, but still there must not be too many bacilli, nor too virulent ones.

For the same reasons the hereditary predisposition no longer makes for the same certainty of action as it does in pébrine. There it resulted from the deposition in the egg of a germ the development of which was assured; here there is no transmission of the germ. We find, it is true, in the stomach of the chrysalis (a stomach

atrophied because it has become useless) the still recognizable forms of organisms which were present in the stomach of the worm, especially of those organisms which have been so little active as to permit the worm to continue its development in spite of the weakening which they have caused. Among these is a small ferment in chains, analogous to the organism figured in the fourth section of Fig. 8, page 70. When one finds this in the stomach of a chrysalis or of a moth he may rest assured that the disease of the *morts-flats* was present at the end of the metamorphosis, and that the egg is suspicious. We may try to find in this direction a criterion of purity which the egg itself is incapable of furnishing, since the egg contains nothing. The heredity which is transmitted is not the inheritance of a germ; it is the inheritance of a function, a reversed vaccination, favoring the invasion of the common germ of the malady, as ordinary vaccination prevents the invasion of the specific germ. Such is, we might say to-day, the inheritance of tuberculosis. If the tubercle organism is not common, if it is incapable of developing outside of the body, a fact of which we are not yet very certain, it is at least widely distributed, and has no need, as we see in case of *flacherie*, of being transmitted through the parents by heredity in order to attack the offspring. All that is necessary is a hereditary feebleness in the functioning of the lungs. The soil prepared, the seed always ready, the disease will always find the occasion to implant itself.

On the contrary, as in *flacherie*, there will be always some hereditary predispositions which will be effaced owing to favorable conditions.

In conclusion, at the end of his *Études*, Pasteur found not only that he had solved the problem which he had undertaken on the regeneration of sericulture, but

had placed on an experimental basis the great questions of contagion and of heredity which dominate all pathology. He was ripe to attack them, and to solve them wherever he should meet them, for his mind was molded upon them. But he was much less advanced in the matter of his technique. He was, in 1870, in a position to grasp the most delicate features of the pathological history of the anthrax of animals but not in a position to approach the question experimentally. It was necessary for him first to perfect his equipment, and his methods of research. The guardian spirit which seemed to have undertaken the direction of his destiny furnished him the opportunity by forcing him into a problem apparently entirely different, the study of beers.





PASTEUR

(From a steel engraving by Manesse, Minerva, Vol. III, 1894.)



## SIXTH PART

### STUDIES ON BEER

#### I

### STUDIES ON BREWING

These studies were begun in 1871, in my laboratory in the Faculty of Sciences of Clermont-Ferrand, and in the chemical laboratory of the School of Medicine of the same town. They were undertaken without any definite aim, simply to occupy the enforced leisure which the Commune and the Siege of Paris gave to Pasteur. He had at once set himself to work to contribute his knowledge which was already great, as his share in the rehabilitation of his humiliated country. He already dreamed of a Pasteur Institute where he would be surrounded by all of his assistants and where he would lead them on to new victories. "I have a head full of the most beautiful projects for work," he wrote me March 29, 1871. "The war has forced my brain to lie fallow. I am ready for new productions. Alas! Perhaps I am laboring under an illusion. In any case I shall make the attempt. Oh! why am I not rich? A millionaire! I would say to you, to Raulin, to Gernez, to Van Tieghem, etc., Come! We will transform the world by our discoveries! How fortunate you are to be young and to have good health! O, that I could begin a new life of study and work! Poor France, dear land of our fathers! Why can I not help to lift you up once more from your disasters?"

While waiting to engage in the great schemes, the

thought of which already haunted him, he allowed himself to be seduced by the idea of studying the manufacture of beer. Was it not possible to make it in France as well as in Germany, and to free us through science from paying tribute to the breweries across the Rhine? Such was the ambition that took possession of him little by little as he penetrated more and more into this difficult subject. To-day we may say that this ambition has been realized as much by the efforts of Pasteur as by the intelligent activity displayed by the French brewers. At the present time, the best French beers are equal to the best German or Austrian beers, and for this progress the French brewers, in the Congress of 1889, gave the honor and credit to the labors and to the book of Pasteur on beer.

This book is not an ordinary book, not a kind of theoretical treatise on brewing. It reflects so clearly the varied preoccupations of Pasteur at this stage of his existence, that I am obliged to draw attention to its somewhat eccentric composition. Of brewing there is very little said. The first chapter shows that the diseases of beer are always due to the development of microscopic organisms foreign to a good fermentation, not at this time a new idea. The last chapter gives the means of making pure and unalterable beers. And it seems, in reality, that this is sufficient, and that one might be content with saying to the brewers: This is why your beers are bad, and here is the means of making good ones!

It was, in fact, in these relatively simple terms that Pasteur stated the problem in the beginning. But he was not slow to see that the question was much more complicated. An egg of a silkworm developed according to a scientific formula is surely a good egg. A beer protected from pathogenic ferments during its manufac-

ture is not necessarily a good beer. Questions of taste enter into the judgment of beer, that is to say, the least scientific thing in the world, the most variable, and the most difficult to grasp. This complex taste, to which each brewery accustoms its patrons, depends at the same time on the original material used, on the yeast, on the water employed in the brewing, and, in a much greater measure than one would believe, on all the varied processes of the manufacture. So that the problem was not that of making a good beer, but of making many good beers, differing each from the other, and reproducing for each brewery the type to which its patrons had become accustomed.

Now, for this work of adaptation and detail Pasteur lacked a very necessary qualification. He did not like beer, and although, as the result of exercise and volition, he finally succeeded in developing a taste for it and a sufficiently trained palate, he remained insensible to differences which the brewers extolled, and which he was sometimes stupefied to see exquisitely appreciated also by his friend, Bertin, who was his neighbor in the Normal School, and who was frequently invited to the laboratory for the tasting séances. At the joyous railleries with which his friend sometimes plied him, Pasteur was disconcerted, knowing that they were carrying him into regions which he did not desire to enter, and he might have renounced immediately this labor of Sisyphus, if he had not had the imprudence to solicit the pecuniary aid of a brewing school which was very large and generous, but with which he had contracted the moral obligation of succeeding in his enterprise.

It is not simply a bad play on words to say that he has never become master of his subject, because he has never been possessed by it. There was no longer that profound absorption in his work so evident in his study

on crystals, on spontaneous generation, and on silkworms. At every instant his thoughts and his actions got away from him without his being conscious of it, attracted by some question which seemed to him more important than the influence of the degree of aëration of the must on the quality of the beer, and it is this which we see in his book, where he attacks and solves a multitude of questions which have only a remote connection with the brewery. The studies on the transformation of species, one into another, on the first origin of the yeasts of the vintage, on the general theory of alcoholic fermentation, fill three-fourths of the book. His obviously desultory style renders its analysis difficult. We shall consider it, en bloc, only as a document which is of great value for the history of the scientific man who composed it.

There is another way of tracing the preoccupations of Pasteur at this time; that is to examine the *Comptes rendus de l'Académie des Sciences*. The Academy served him both as a tribune from which to reply to his opponents without, and as a field of combat for the discussions, sometimes picturesque, into which he entered with some of his confrères. All this part of his life forms an animated picture. Let us endeavor to trace the principal facts without following strictly the chronological order.

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## II

### TRANSFORMATION OF ONE SPECIES INTO ANOTHER

There is in the beginning one part with which we are already familiar, through having encountered it in its proper place. That is the whole discussion with Bastian on spontaneous generations, and with Liebig on the rôle

of ferments in fermentation. We have seen that Pasteur had come to know that the air was not that receptacle for germs, that redoubtable enemy which he had hitherto supposed it to be, and had convinced himself that, provided the liquids were well sterilized in the autoclave and the flasks in an oven, it was possible to work with some security in contact with air, and not have to fear too much the entrance of germs from this source. All our present technique has come from these ideas. Personally Pasteur was indifferent to perfection of technique; the complexity of his apparatuses was of little importance to him. He only required that they should be reliable, and answer the questions he asked without ambiguity. But accuracy and facility or rapidity of question and answer may go hand in hand. This is the rôle of a good technique. That which has come out of the laboratory of Pasteur was the offspring of the ideas and discoveries of the master; but it is only just to say that it was created by the three collaborators whom Pasteur had the good fortune to encounter at this time—Joubert, Chamberland and Roux.

Pasteur needed another thing for approach to the domain of pathology, which every circumstance invited him to enter. He saw the germ theory inspire the works of Davaine on the anthrax bacteridium, the startling experiment of M. Chauveau on castration by subcutaneous torsion (*bistournage*), Alphonse Guérin's new method of dressing wounds, the researches of M. Guyon on antiseptic washings of the bladder and of the urethra. He had applauded in 1871 Dr. Déclat's successful experiments in the antiseptic dressing of wounds; he did not yet know the work of Lister in antiseptic surgery, which has opened a new era, but he was not slow in finding it out and admiring it. But in order to approach the promised land of which he dreamed, and especially

to do so with security, he had need of an equipment of facts and ideas which he did not yet possess, and which his opponents forced him to acquire.

The most remarkable example I can cite in support of what I wish to say comes from the discussion with Trécul, who, renewing an opinion introduced into science by Turpin and later supported by Bail, Berkeley, Hoffmann, Hallier, admitted the transformation of microscopic species, one into another. This was denying the specificity of the germ established by the first labors of Pasteur on fermentations, and Pasteur had combatted this opinion, beginning in 1861 in the *Bulletin de la Société philomathique*. To comprehend what obscurities this theory would have introduced into microbial pathology, it is sufficient to recall that a denial of the specificity of the germ would have controverted the present day belief in the specificity of disease. It was, therefore, important that it should be rooted out of all minds.

Unquestionably, it was not the demonstrations of Bail, of Hoffmann, or even those of Trécul which could give credit to this theory. All these eminent botanists were poor experimenters, going out to meet sources of error, not to bar the way, so to speak, but to open it up to them. But favoring this idea of the mutability of species was the doctrine of spontaneous generation, which found in this mutability one of its arguments. There were the new ideas introduced by Darwin and the school of evolutionists. Finally, and this was more grave, Pasteur himself, the greatest authorized exponent of the opposite school, or rather of the experimental method, rejected, in the name of experimentation, the transformation of yeast into *Penicillium glaucum*, but accepted that of the *Mycoderma vini*, or flowers of wine, into an alcoholic ferment under certain conditions.

On sweetened wine or must of beer, exposed in a shallow porcelain basin, he sowed some mycoderma which formed a pellicle on the surface. He then submerged this pellicle, thoroughly shaking the liquid in order to dislocate and moisten all parts of it. Then he introduced the whole into a flask which he filled completely full and which he closed with a stopper to which was attached a tube, the opposite end of which opened under water so as to allow no contact of air with the liquid. In this closed flask he saw a true fermentation take place, which he attributed to the transformation of the mycoderma cells into yeast.

At Clermont, where Pasteur did me the honor of working in my laboratory, we repeated this experiment several times, and as I was naturally more intransigent than he, being his pupil, I refused to yield to this proof, and I objected to the possible presence of globules of yeast derived from the air, from the water, or from the flasks before or after the filling, in spite of the precautions taken to avoid it. Pasteur resisted because, in his mind, this fact was related to other ideas which we shall encounter soon, and which are relative to the general theory of fermentation. The experiment, furthermore, sometimes succeeded with a clearness which made it convincing and closed my mouth. In short, Pastuer had reported his conviction in Paris, and it reappears several times in his Notes of 1872 and 1873 before the Academy of Sciences.

If I recall this fact, it is because Pasteur loved to cite it himself as an example of the ease with which the least preconceived idea leads even the most alert observer into error. Thus it is that he has taken pains to recount how he discovered his self-deception. It is interesting to see his mind at work in one of the thousand details of his scientific life.

“In the experiments conducted as I have just described, the yeast which comes into existence, and which very promptly causes an active alcoholic fermentation, is introduced originally by the atmospheric air, which allows the germs to fall either upon the mycoderma pellicle or the objects which are used during the succession of manipulations. Two circumstances of these experiments gave me warning of the existence of this cause of error. It sometimes happened that I found among the cells of the mycoderma in the bottom of the flasks where I had submerged the flowers of wine, some large spherical cells of *Mucor mucedo* or *racemosus*, yeastlike cells with which we shall soon become familiar in studying this curious mold. Since there is present *Mucor mucedo* or *racemosus*, although I had sown only *Mycoderma vini*, it must be, I said to myself, that one or several spores of this *Mucor* have been introduced by the ambient air. Now, if the air brings the spores of *Mucor* into my operations, why would it not bring the cells of yeast, especially in my laboratory? Further, more, it happened that in a number of the experiments which I repeated many times, under the pressure of my doubts, and in which I did not grow weary of searching for this desirable transformation which accorded so well with the physiological theory of fermentation to which I had been led, some had a negative result, that is to say the transformation of the mycoderma into yeast did not occur, although the conditions were as similar as one could wish to those of the experiments in which I saw it take place. Why, thought I, this inactivity in the cells of the mycoderma? Even in the most favorable cases of the supposed transformation it happened without doubt that a multitude of cells of *Mycoderma vini* did not become yeast cells, but how admit that among the billions of submerged cells all were



unfitted for transformation, if this transformation were really possible?

“It was, then, to avoid this embarrassment, that I resolved to modify entirely the conditions of the experiment, and to apply to the research which I had in view a culture method which would suppress completely,

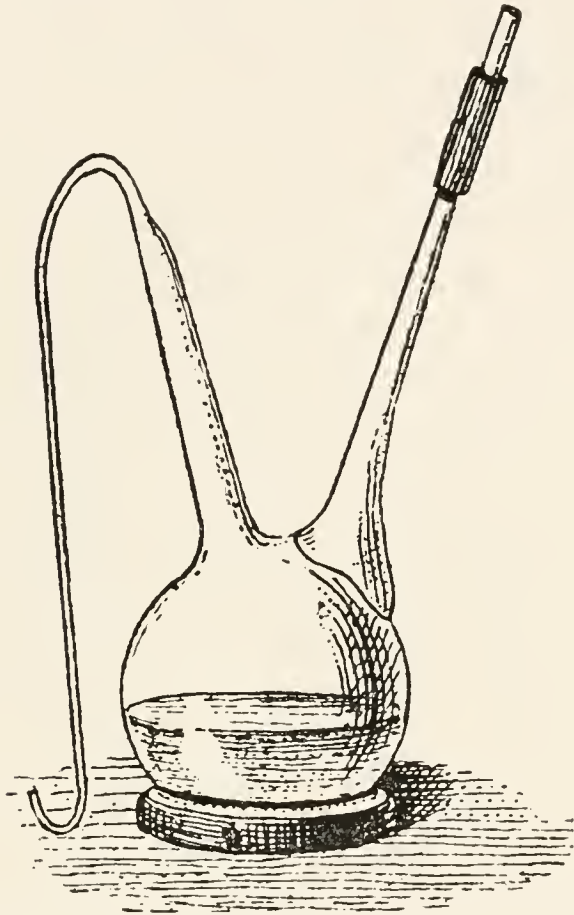


FIG. 14.—Flask used by Pasteur in his study of the transformation of species.

or at least very nearly, the sole cause of error which I had encountered, that is the possible falling of germs or of yeast cells from the air during the manipulation.”<sup>1</sup>

To carry out this idea, Pasteur added to the flask with the curved neck which he had used in his studies on spontaneous generations, a second tubulure (Fig. 14)

<sup>1</sup> *Études sur la bière*, p. 118.

permitting the inoculation of the liquid by removing the glass stopper which closed the rubber tube attached to the straight tubulure. In this flask the culture is in contact with air. When there is need of provoking a fermentation in the absence of air, the straight tubulure is connected by means of its rubber tube with a matrass sufficiently small for the liquid to fill it completely. In order to make with this apparatus a study of the transformation of the mycoderma into yeast, it is

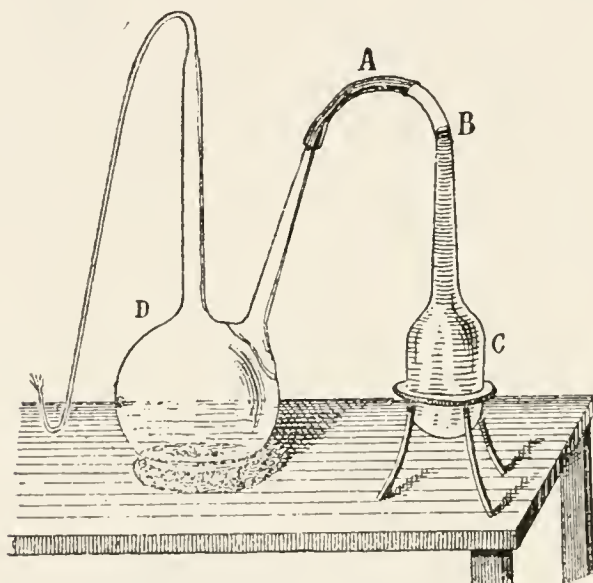


FIG. 15.—Apparatus used by Pasteur in his study of alcoholic and other fermentations.

sufficient to sow with the flowers of wine an alcoholic liquid, or a sugar solution placed in *D*, and to pour it immediately, when the pellicle has formed, into the matrass *BC*, where it finds the conditions of great depth and of small free surface existing in the flask of the first experiment (Fig. 15). The details of the manipulation necessary to realize this transfer in the absence of all exterior germs are of little moment. The apparatus is furthermore, complicated and has been advantageously replaced since. It suffices, however, to attain the

desired end, which is the comparative study of the same mycoderma on the surface and in the depths.

“Never again,” continues Pasteur, “did I see the yeast or an active alcoholic fermentation, following the submersion of the *flowers*, either in the flasks or in the matrasses connected with these flasks. . . . At a time when ideas on the transformation of species are so easily adopted, perhaps because they dispense with rigorous experimentation, it is not without interest to consider that in the course of my researches on the culture of microscopic plants in the pure state, I have once had occasion to believe in the transformation of one organism into another, in the transformation of the *Mycoderma vini* or *cerevisiæ* into yeast, and that, this time, I was in error. I did not know how to avoid the cause of error which my justified confidence in the germ theory had led me to discover so often in the observations of others.”

The same flask with two tubulures served Pasteur to show that the alcoholic yeast is not transformed into a lactic ferment, as J. Duval said, nor into *Penicillium* or *Aspergillus*, as Hoffmann maintained; that this yeast, itself, did not come from the transformation of the spores of *Penicillium*, as Trécul said; nor furthermore did the *Mycoderma aceti* yield the bacteria which Béchamp believed he saw derived from it. In short, the idea of species was saved for the time being from the attack which was directed against it, and it has not been contested seriously since that time, at least on this ground.

## III

## ANAËROBIC LIFE OF AËROBIC SPECIES

In exchange, Pasteur had the sorrow of seeing ruined one of the arguments most favorable to his physiological theory of fermentation. But he ought not to have been slow to congratulate himself upon this slight check, because behind the fallen argument there arose another still more convincing, which the first had masked. It sufficed him, in order to find it, to repeat with *Mucor mucedo* the preceding experiments.

Bail had announced in 1857 that this mucor which lives the life of an aërobic plant, when in contact with air, can, when submerged in the absence of air, produce a very active alcoholic fermentation.

There are found then in the liquid, instead of more or less septate mycelial filaments which serve to some extent as roots for this plant, chains of round or oblong cells, which Bail had taken for the cells of yeast of beer. Repeating these experiments under the pure-culture conditions which we have described, Pasteur determined that these affirmations were exactly true. Submerged and in the absence of air, the mycelium of the fungus becomes very much septate, being transformed into a chain of cells; simultaneously bubbles of carbonic acid are given off, and alcohol is present in the liquid. What is the explanation of this? Is this mucor then an exception? Can it undergo transformation into yeast? This was the opinion of Bail; but we shall soon see how much was gained by going below the surface of this question. From this apparently insignificant fact, Pasteur has evolved a whole theory of fermentation.

In order to place these phenomena in their proper light we shall suppose that Pasteur treated them as



PASTEUR

(From a common photo.)



was his ordinary custom, that is, that immediately following their discovery, he combined them in a synthetic experiment. If he had wished to pursue that course in this case, the following undoubtedly would have been his method of procedure.

Into a series of flasks with two tubulures like those we have just described, each one-third filled with sterilized must of beer, he would have introduced, by removing for an instant the glass stopper closing the rubber tube, a small platinum wire which had been flamed and passed over a spore-bearing culture of the mucor. He would then have flamed the stopper and replaced it.

Let us take for example the three Mucedinæ studied by Pasteur, *Penicillium glaucum*, *Aspergillus niger*, and the *Mucor mucedo*. That makes three flasks. At the end of 24 or 48 hours, the spores introduced by the platinum wire will have produced a branching mycelium, which if well aërated produces aërial branches surmounted by tufts of young spores; but at the bottom of these flasks, which communicate with the exterior only by means of a long capillary neck, our mycelia have only an insufficient quantity of air and they fruit little or not at all, but nevertheless in time they oxidize completely the sugar on which they live.

Before the sugar has disappeared let us connect as before the straight tubulures of each of the flasks with a smaller matrass which the liquid will fill up to the neck, and let us pour the liquid into it. In its new receptacle, this must of beer will be less exposed to air than before. We might even say that it has no air at all at its disposal, for the mycelium has caused all that which was in the solution to disappear, and has replaced it by the carbonic acid which, being given off from the surface of the latter, prevents the arrival of new oxygen. Under these conditions, we find that the mycelium of

Penicillium rapidly suspends its action and becomes inert; the mycelium of *Aspergillus* continues a little longer to consume the sugar, but its growth is also soon arrested. Only the mycelium of *Mucor* endures for several hours this deprivation of air. It becomes foamy as the result of an ebullition, abundant at first then more slow, of bubbles of carbonic acid; and we find in the liquid very perceptible quantities of alcohol. In short, to the complete combustion which the mucor gives in contact with

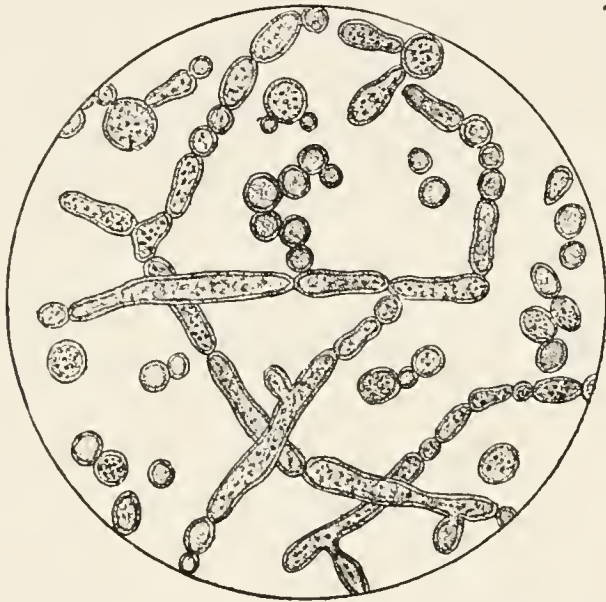


FIG. 16.—Yeast-like forms assumed by *Mucor mucedo* in the absence of air.

air, there succeeds, without transition and without apparent difficulty, at least in the beginning, a partial combustion in the form of an alcoholic fermentation.

Singularly, the mycelium of the plant becomes modified under these new conditions of existence; that of the *Penicillium* remains almost as it was; that of the *Aspergillus* segments and in place of the branching filaments has chains of cells. It is in the mycelium of the *Mucor* that the changes are the most marked. As long as the fungus is living as a mold in free contact with air, its



mycelial filaments are slender, branching, and intertwined, but when it becomes a ferment as the result of an insufficient supply of air, the hyphæ segment, separate, enlarge, and finally are transformed into chains of large, round, or slightly oval cells (Fig. 16) which, in reality, resemble large cells of yeast. Bail had believed in their transformation, but Pasteur shows that when these supposed yeasts are introduced into aërated must of beer they do not produce alcoholic fermentation: they reproduce the *Mucor*. There has not, therefore, been any transformation of species; there has been only an adaptation to a new life, with a change of form corresponding to change of functions.

When he had reached this point, Pasteur might recall that there are analogous changes in the mycoderma of wine when submerged in a sugar solution. The cell becomes more turgescient, its protoplasm less granular (Fig. 13). The mucor and the mycoderma, so different in form, resemble each other, therefore, in their nature. In the case of both, and of a certain number of other lower species, the fermenting property, that is to say the ability to break up sugar into alcohol and carbonic acid, appears to us, therefore, not as a specific property but as a transitory faculty related to the conditions of existence, and we may briefly sum up the foregoing by saying that *fermentation is life without air*.

When Pasteur gave utterance to these facts before the Academy of Sciences, he was not understood at first, and his opponents shouted cries of victory. This modification of form accompanying a modification of properties was transformation, as much as that of Hoffmann, or Turpin, or that of Darwin. No, Pasteur unceasingly repeated, it is not a question of a transformation of species but of a general physiological law which is applicable alike to all living species and respects

their individuality. It is a question of a functional elasticity of the cell, permitting it to adapt itself without changing its nature, *to be* and *to become* according to varied conditions of existence. We see to what heights he had raised the debate: by changing the mode of interpretation of facts already known, he caused them to give birth to a new theory.

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#### IV

#### AËROBIC LIFE OF ANAËROBIC SPECIES

The preceding facts had in reality a bold counterpart. We have just seen that some species, aërobic under ordinary conditions, can lead an anaërobic life for a greater or less length of time. In like manner we ought to be able to acclimate a species which is ordinarily anaërobic to an aërobic life.

Such is the yeast of beer. Let us try first to ascertain just how far it can go in its anaërobic life by sowing it in a nutrient solution which we have completely deprived of oxygen, it matters not how. In this disaërated medium the yeast lives, but feebly; its development is slow, and the fermentation takes a long time. But it comes to an end, and if, when it has terminated, we investigate the relation between the weight of the sugar transformed and the weight of yeast present we find a very high figure, of 150 to 200. If, for example, we work with 100 grams of sugar, we shall see that from 5 to 7 decigrams of yeast have been sufficient to transform it into alcohol and carbonic acid.

Let us now give to the yeast a little more air. Let us sow it in a fermentable aërated liquid, contained in a flask which we shall not fill completely, so that the yeast

has at its disposal for its needs the oxygen dissolved in the liquid, and a little free oxygen in the air of the flask. This time life is more active, fermentation more rapid, reproduction of the yeast more abundant, and for 100 grams of sugar transformed we have about 1.5 grams of yeast produced.

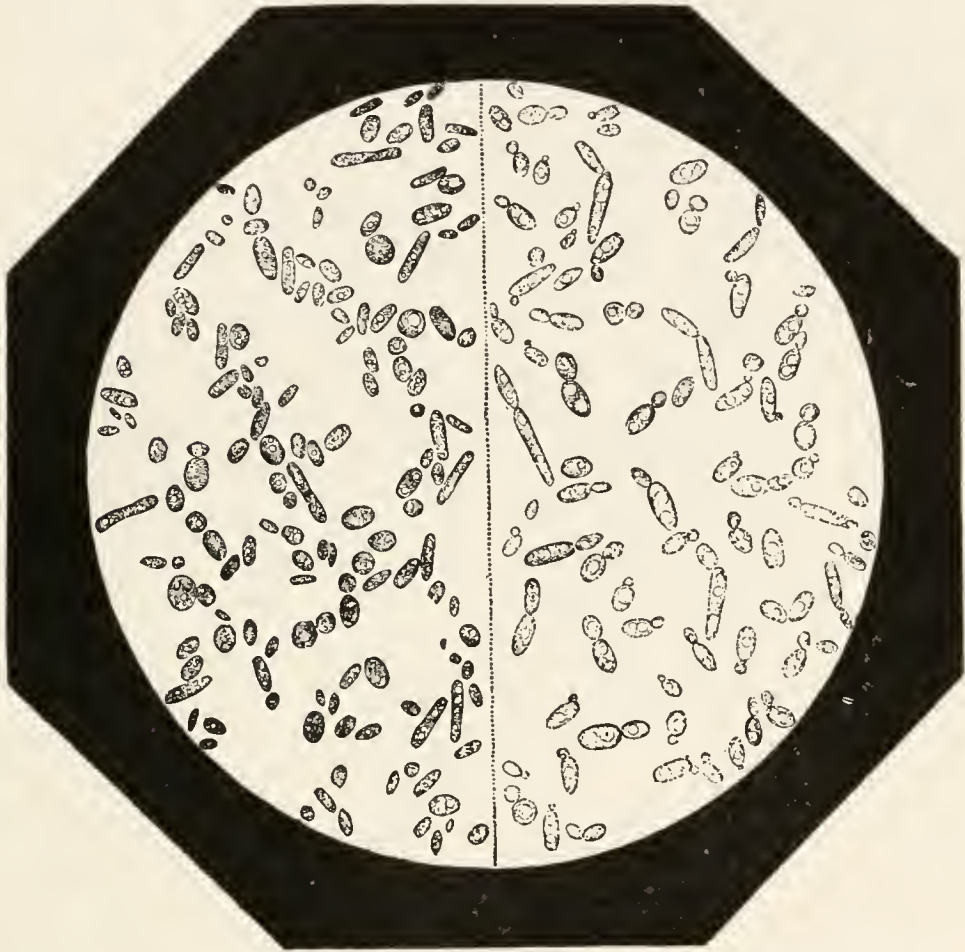


FIG. 17.—Left side: disjointed cells of old yeast. Right side: Their rejuvenation in a sugared must.

Let us go a step further in the process of aëration. Let us spread out our sugar solution over a broad surface or shake it in contact with air, so that each yeast cell finds itself constantly in contact with the free oxygen of which it has need. This time, the sugar disappears rapidly; it no longer gives alcohol, or at

least gives very little; it is a complete combustion which has followed the incomplete combustion of the preceding experiment in the same way as an incomplete combustion followed a complete one in the case of the mucor when deprived of air. Finally, a last analogy: the yeast, like the mucor, multiplies and increases markedly in weight in contact with air, so that, this time, for 100 grams of sugar used, we find 20 to 25 grams of yeast produced.

Some modifications of form accompany here also these changes of function. The yeast in contact with air is less full of cavities, has a much finer content, and is younger in aspect, as the comparison of the two halves of Fig. 17 shows.

In this very aërobic existence, the yeast, therefore, approaches the Mucedineæ. It differs from them in that it can lead the anaërobic life, to which it is adapted for a very much longer time, than even the Mucor. But here also, the appearance of the ferment-character accompanies life without air.

So that in the presence of the general character of these facts, Pasteur had been led to ask himself the following question: Can we admit that the yeast and the other plants capable of becoming alcoholic ferments which absorb and consume oxygen so actively when they have it at their disposal, cease to have need of it when it is refused them, and in this case change completely their mode of existence? If we reply, "Yes," to this question, then there is no relation between aërobic and anaërobic life. These are two different living organisms which succeed each other in the same protoplasm and within the same cell-wall. If we admit, on the contrary, as it is evidently more natural to do, that the needs of the cell in its two modes of existence remain the same, and that only the means of satisfying

them change, then the appearance of the ferment-character is connected with the absence of oxygen, and we are led to think that if the yeast and the analogous plants can act thus on sugar during their anaërobic life, it is because they have the ability to obtain from it the oxygen which they need, the oxygen which serves, furthermore, for their respiration, and which is given off at once, more or less completely, in the form of carbonic acid.

According to this conception, every living cell having need of oxygen, if deprived of this gas in a free state, and if able to obtain it from substances which contain it in a combined state, would be a *ferment* for these substances. Here is a theory of fermentation very directly related to the facts, as we have come to see, and, furthermore, very suggestive, for, if it notably enlarges the field of cellular ferments, it at the same time restricts the field of fermentable substances by showing that only those substances can be fermented which are capable of furnishing to their ferment the oxygen which the latter uses by burning a part of it. Every fermentable substance is capable, consequently, of undergoing an internal combustion, giving off heat thereby, for since there is a life to maintain, it is necessary that there be somewhere a source of energy. The living organism does not produce it; it consumes it in order to build up its tissues, in order to make them live. So that a fermentable substance, before producing heat by undergoing an internal combustion, becomes, in a certain measure, comparable to an explosive body, gun-cotton or nitroglycerin, which burns little by little in the laboratory of the yeast cell. Here is the very simple conception which Pasteur called the physiological theory of fermentation.

We are forced to believe that it was not clear, since,

leaving aside the *Dii minores*, such men as Cl. Bernard and Berthelot did not succeed in comprehending it. It is true that only with difficulty do great minds understand one another. We have seen Liebig remain deaf to the arguments of Pasteur and blind to his demonstrations; we are going to see the same struggle in the dark follow between Bernard, Berthelot and Pasteur.

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## V

## IDEAS OF CLAUDE BERNARD ON FERMENTATION

The history of the discussion with Bernard is curious in that Bernard took no part in it, and that Pasteur, was obliged to debate with a shade. This was very painful to him. Bernard had been while he lived, I will not say a confidant, but a friend with whom he loved to chat during the séances of the Academy of Sciences. These séances are of value only because of these chats, and it would be beneficial to allow them to go on freely in the salon, while the Bureau proceeded, in another part of the building, with the official reception of notes and memoirs. We may well believe that between Bernard and Pasteur, who occupied neighboring arm chairs, there was no question of religion, politics or scandal. They spoke of science to the great benefit of themselves and of others. Theirs were two powerful minds, concentrated in their work, the more capable, consequently, of a mutual appreciation and understanding, but gaining by an exchange of blows and a sharpening of wits one against the other.

Bernard, toward the end of his life, had been led to a conception of the phenomena of life which seemed then and still seems a little strange. He conceived that there

were in the living organism two kinds of phenomena: the phenomena of construction or synthesis, which alone he considered as truly vital, and the phenomena of organic destruction, which he considered to be of a physico-chemical order. In a word, it was life alone which was constructive, leaving to the forces of death the work of destruction. These phenomena, different in origin, were, nevertheless, not separated in space and time. Bernard admitted that there were phenomena of destruction in the living cell, and that whenever a muscle contracts, a gland secretes or the mind works, there is a portion of the tissue, muscular, glandular or cerebral, which is destroyed. But although simultaneous and correlative to a certain degree, these phenomena of synthesis and decomposition were none the less of different essence, and not obedient to the same mechanism.

Pasteur, in his refutation of these ideas, does not seem to me to have perfectly understood them. Bernard does not believe at all as Pasteur thought,<sup>1</sup> "in a forced opposition between the phenomena of life and synthesis and the phenomena of death and destruction, between life, properly speaking, and fermentation." At least he nowhere says so. On the contrary they were, according to his conception, two machines which concurred in the same work, propelled by two different motive forces. When death occurs and the *life-motor* ceases to act, the second motor which is fed by combustions and fermentations, remains in action, and it is that which, in ways purely physical or chemical, having no longer anything vital, presides at the return of dead matter to the ambient nature.

This conception did not contravene, as one might believe at first, the demonstrations of Pasteur on the

<sup>1</sup> Examen critique d'un écrit posthume de M. Bernard sur la fermentation. p. 47.

subject of the non-existence of spontaneous generations, and on the subject of the rôle and multiplication of the ferment in fermentations. Bernard was very respectful when face to face with facts, but when he reflected on them he gave himself, as he had every right to do, a great liberty of interpretation. Not because one salutes another is he obliged to think well of him. Now, on reflection, Bernard came to approach, little by little, the stand taken by Liebig, and asked himself, for it was still only the period of hypotheses and of brain-work which preceded that of laboratory work in his case, asked himself, I say, whether, perchance, it was not in virtue of the second mechanism which he predicated, that is to say by disassociation and destruction, that the microbes caused the destruction of organic matter.

Unquestionably a mind like his had the right to put these questions since it was in his power to solve them. If he could show that the best-known phenomena of organic destruction, the transformation of sugar into alcohol and carbonic acid, could be produced entirely without the intervention of yeast or even of living cells, by the natural play of forces exterior to the cell, and subject only to the laws of physics and chemistry, what a precious confirmation of his preconceived ideas! These physico-chemical forces could not, it is true, be common forces taken by chance from the ambient nature. Pasteur had shown too clearly, apropos of spontaneous generations, that, reduced to these forces alone, the transformation of dead matter was a very slow process. But if living cells are needed to accelerate this transformation why should these cells not act by manufacturing and secreting, on the vital side of their organization, substances capable then of acting outside of the cell, and in a physico-chemical way? The yeast secretes a diastase which, outside the cell, can invert cane-sugar. Why



should it not secrete another diastase capable of transforming sugar into alcohol and carbonic acid?<sup>1</sup>

Such was, at least as far as we can see, the cycle of ideas which Bernard made a beginning of submitting to experimental verification at his country house at Saint-Julien, at the time of the vintages of 1877, some months before his death. Without saying anything about it to any one, he had written down, a little carelessly, his first results and his new projects for experiments in the loose leaves of a manuscript which was found after his death, and which his friends believed worthy of publication. It is always necessary to distrust one's friends, especially when one is no longer there to watch them. Posthumous writings have never augmented the glory of any one, and the publication of these few pages of notes, which Bernard had very wisely concealed at the bottom of a drawer, had not, in my opinion, any pretext or excuse. The kind of general ideas in the light of which they had been conceived and written was sufficiently well-known by the recent publication of the work *Sur les phénomènes de la vie communs aux animaux et aux végétaux*, the proof of which Bernard had carefully corrected at Saint-Julien in 1877. If the ideas of the master had undergone a little change since then, it is not to be observed in the sybilline phrases of the manuscript. In running through them to-day, it seems evident that Bernard could not have considered his work as anything more than a blow given with a mattock in order to test the soil before beginning his labors.

<sup>1</sup> We now know that it does do this, but that this enzyme (called Zymase) can be obtained for study only by crushing the yeast under high pressure. *Trs.*

## VI

## DISCUSSION OF THE IDEAS OF CLAUDE BERNARD

Assuredly, in the presence of these confused experiments, published without the consent of the one who made them, Pasteur might have replied only with that Olympian silence which Bernard would certainly have maintained in like circumstances. He preferred rather to do what he had always done, to go straight to his adversary at the risk, he said, of encountering M. Berthelot behind the manuscript of Bernard. To the latter he replied first: "Your diastase which makes alcohol? Do not think that that embarrasses me. I shall be happy to salute it, but I should like to see it first. I have searched for it and never found it. In some recent experiments which took place under your eyes, at the Academy, and which met with your approval, I put some cells of the grape, taken from the interior of the fruit, into a sugar solution in contact with pure air and I have found neither diastase nor alcohol there. How is it that you, to whom I have so often spoken of it, have forgotten or been unmindful of these experiments?"

To which the shade of Bernard might have replied: "Reassure yourself, my friend, I am not unmindful nor do I forget anything! But because you have not seen a thing, does not prove that this thing is impossible. In order to demonstrate the existence of this diastase I make other conditions than yours. I take grapes which are beginning to decay, because for me the decay is a maturity, not advanced, as you make me say without, in your turn, at all understanding my point of view, but anticipatory, that is to say, premature. A decayed grape is one which is mature before the others, and in which are beginning the phenomena which only mani-

fest themselves later in its sound neighbors. In these decayed grapes I find alcohol. I find it also, at least so I believe, in the dry grapes, and I see there no cells of yeast. Thence, the idea of my diastase. It may very well be that this secretion of diastase takes place only once, and that I came at a fortunate moment, while you were too early or too late, but that will not hinder us from remaining good friends.

“Note furthermore,” Bernard might have continued if he had been able to plead his own cause, or if he had had an advocate, “that my conception is in accord with some of the experiments which you cite in support of yours. MM. Lechartier and Bellamy before you have seen fruits, put in closed flasks in the presence of air, begin by absorbing oxygen, then give off carbonic acid, and, furthermore, produce alcohol by an interior fermentation accomplished without the aid of any yeast cell. It is one of the experiments which you cite in support of your ideas of life without air. I consider it as a score for me, and I say that the results of MM. Lechartier and Bellamy have to do only with the decay of fruits in confined atmospheres. But if they were rotted in contact with the air it would be the same, as my results with grapes testify, and as, I hope, the experiments which I intend to make on apples will also testify.”

“But,” responded Pasteur, “you who have such a good memory for the results of MM. Lechartier and Bellamy who, moreover, are in accord with me, how is it that you have forgotten my experiments in which, instead of waiting until they shall have consumed the oxygen of the air with which they are in contact, I plunge the fruits immediately into carbonic acid, and see the formation of alcohol begin there immediately. Can it be a question of decay in this quick experiment

when the fruits come out of their matrass healthy, of good flavor and sometimes, as in the case of prunes, more firm than when they entered? Do you not know, furthermore, that M. Müntz has made the same experiment on entire living plants, which produce alcohol when made to live for some time in carbonic acid, and which resume their ordinary existence, when restored to the air, with as much facility as a traveller who comes out of a tunnel and finds once more the air and sunshine?" And thus the discussion, which I have made a dialogue, and which was a monologue, might have been continued a long time without bringing forth any new arguments or elements of conviction, for the experiments of Bernard were too vague to signify anything, and Pasteur has not added anything new to this point of the discussion which has remained sterile.

It was the same with a lively and somewhat passionate dialogue which took place between Pasteur and Berthelot on the work of Bernard. This, however, does not lack interest. There is always interest in a strife between men of this stamp. There is always profit in hearing them develop their arguments and discuss the ideas of their adversary. But here the opponents were not equal. One of them led into a field which was not his own, fenced a little at random, and sometimes laid himself open to a thrust. As soon as he left the least spot unguarded, the blow of the button came straight, promptly, irresistibly. It was truly a curious passage at arms, but as it did not bring forth any new facts, its interest has disappeared. Pasteur came out of it more fixed in his ideas, and Berthelot, apparently, without having yielded any of his. This should lead us to distrust all discussions, even scientific ones.

It is a common belief that a scientific discussion has a greater chance of coming to something than any other,

because it takes place in the *domain of facts*. But a fact, even of the physical order, is nothing by itself. It becomes something only when it passes into the state of an intellectual fact, by traversing an intelligence the imprint of which it receives. It is then related to another fact, sometimes this and sometimes that, and thus are born a certain number of conceptions or of theories, which make more or less proselytes. There are certain facts, or certain groups of facts, on which tradition, habits of education and the general debility of intelligences have set everyone in accord, and which are considered as verities, as belonging to the foundations of science, until the day when an investigator more bold than others thinks of taking a look at them, and contradicts them. Then they disappear, or are interpreted differently, which overthrows the accepted theories.

If the verities of the rear-guard are so subject to caution, what must be the case with those of the advance guard, those which are the recent conquests? For these there is no rule and tradition; every person can interpret them according to his liking. Thus, in a discussion with Pasteur, Frémy had had on this subject an idea of astonishing candor. He proposed to his adversary that he would accept all his, Pasteur's, facts, provided Pasteur would accept all his, Frémy's, interpretations. This was to demand everything, for we do not discuss facts, but their interpretations. Whence it results that even a serious discussion between two good minds has no chance of leading to anything, so long as it remains in the domain of facts already acquired. It is useful only when it leads the adversaries to investigate and produce something new. If they both succeed, they are both right, even when they are not in agreement. If they do not venture, or if neither one reaches any results, the discussion may amuse the gallery,

instruct it, perhaps even give rise to some new ideas there, but it is sterile for those who have taken part in it. A savant is not the routine man of the study; he is the man of the laboratory.

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## VII

### ORIGIN OF THE YEASTS OF WINE

Pasteur had entered into his own domain in the discussion of a part of the posthumous work of Bernard. He wished to elucidate a question which he had had at heart since the beginning of his studies on alcoholic fermentation, to which he has returned many times, but which he has not completely solved, because it is difficult. That is the question of the origin of yeasts.

In his *Études sur la bière*, he had very much enlarged the conclusions of his first memoir of 1862, published in the *Bulletin de la société chimique*, and had shown that there existed a great number of yeasts, different not only in form, but also in their physiological properties and in the various tastes which they communicate to the liquids which they ferment. But whence come these numerous yeasts? Are they special vegetative forms of a microscopic plant other than the yeast, and known under another name? And if so, what is this plant? or rather, what are the different plants which give birth to the different yeasts? If, on the contrary these yeasts have no other form of reproduction than that with which we are familiar, how, in nature, do they pass the winter and the periods during which there are no sugary solutions to ferment? Experiment teaches, as a matter of fact, that, when dried and exposed to the air, the various yeasts rapidly lose their vitality.

The question does not arise regarding the cultivated yeasts, those for example which the brewer transfers from vat to vat in all seasons, as has been the custom for centuries, but applies only to the wild yeasts, which reappear at the appointed place every year, to ferment the grape crop. For the wine-manufacturer does not



FIG. 18.—Top yeast of the brewery.  
Old. Rejuvenated.

add yeast to his casks, and yet the ordinary fermentation begins freely and actively, sometimes in 24 hours. At what moment do the stems of the cluster and the newly formed fruits become charged with these germs?

Experiment has shown that this occurs late in the season. As long as the grape is in the stage of verjuice

which, in the Jura, is toward the end of July, we can introduce into a fermentable juice bits of the fruit and fragments of the stem of the cluster without any fermentation of this juice, provided we work carefully and avoid every chance of the introduction of germs other than those which we wish to study. But, as the grape ripens and the day of the harvest approaches, there is an increase in the number of grapes and fragments of the stem which carry the yeasts with them into the juice in which they are sown. The wood of the cluster is at this time more charged with germs than the fruit, which is, itself, more richly supplied than the wood of the branch or the twigs of the vine. Even at the moment of the harvest, not all the grapes are carriers of germs capable of fermenting them, and one may crush them individually and even by twos in sterile flasks, that is to say, place their superficial pellicle in contact with their juice without seeing the latter ferment. Then, after the harvest, when we have made it by collecting only the grapes, leaving behind the stem of the cluster, the germs of yeast upon the latter gradually become fewer and fewer, so that by December and throughout the winter there are none at all. There remain on it only the germs of molds.

This first question when solved gave rise to another. In what state, on the surface of the berry and on the wood of the stem, do we find these germs of yeast, the existence of which we have just demonstrated? Washing these surfaces with a clean badger's-hair brush, we obtain a clouded drop which, under the microscope, shows nothing resembling yeast. We see there only numbers of corpuscles (A, B, Fig. 19) of a more or less deep brown color or reddish yellow color, with thick and opaque walls, and other more translucent cells, none of which give the idea or present the aspect of the familiar yeasts.



But let us leave this dust, evidently living, in a thin layer of sugar solution exposed to the air under the microscope, and we shall see come forth in profusion from certain groups of the brown corpuscles, cells ( $A_1$ ,  $A_2$ ,  $B_1$ ,  $B_2$ , Fig. 19) or branching filaments which at once bud and segment into cells. Now these cells are yeast cells, for, once rejuvenated in contact with air and sown in a sweet must, they produce in some hours an active alcoholic fermentation.

Pasteur must have felt a profound joy in discovering

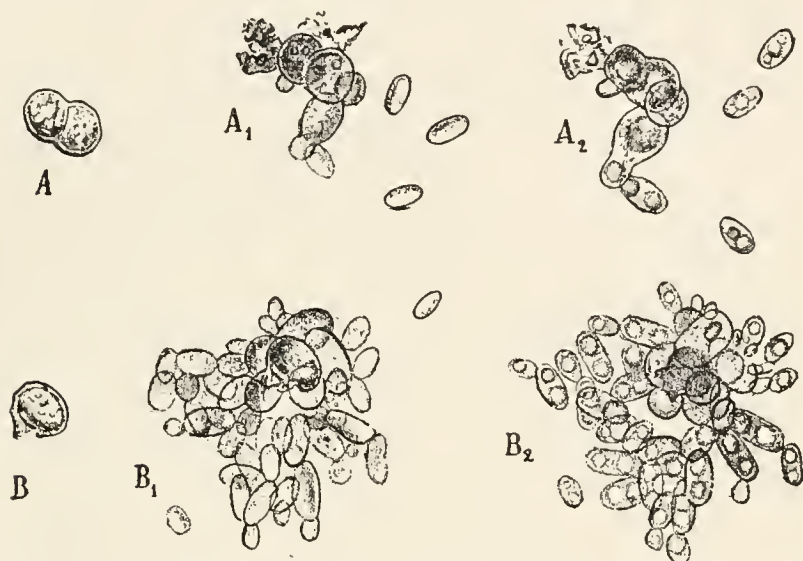


FIG. 19.—Thick-walled brown cells that give rise to wine yeasts.

these facts, for, with his usual perspicacity, he must have seen immediately the solution of a problem which had been in his mind for a long time, and of which he had many times tried in vain to find the solution. The origin of this difficulty was the experiment of Gay-Lussac which we have described, and in which this scientist had seen some bubbles of oxygen produce fermentation in the juice of grapes crushed in a test-tube under mercury and remaining inert up to that time.

It is here that we can find a proof of the truth of that

which I have affirmed above. Here is a fact: fermentation takes place. All the world accepts it, but how interpret it? The proof that this is not easy, is the fact that it has received four different interpretations, namely, one by Gay-Lussac, one by Liebig and two by Pasteur.

Gay-Lussac was content to say: "It is the oxygen which sets the fermentation going." Liebig, after him, had searched more profoundly and said: "It is the albuminoid matter of the must which needs oxygen in order to enter into decomposition and to acquire the properties of a ferment." For 30 years this interpretation had enjoyed the honors and credit of a demonstrated truth. Pasteur arrives on the scene and says: "The albuminoid matter has nothing to do with the phenomenon. The ferment is a living organism which comes from a germ, and if the air has conveyed into our test-tube a cause of fermentation, it is because it has brought a germ there."

It was surely not without some regret that he came to this conclusion, because this view furnished a weapon to the partisans of spontaneous generation, and permitted them to say: "How is this? Do you admit the germ of a ferment in each bubble of air? Then what becomes of your conclusions relative to the rarity of germs in the atmosphere?" This objection embarrassed him only a little; but if he had had a discussion to support on this subject he would only have been able to multiply words upon it. He must have uttered a cry of joy when he was led by experiment to a fourth interpretation: The germs of the yeast are carried by the grape-berry; they are inert as long as they are deprived of oxygen and it is the introduction of the bubble of gas which gives the whipstroke of departure for existence in a state of fermentation.

It is a singular thing that all these results, so curious

and so new, known for a year through the publication of the *Études sur la bière*, had been forgotten in 1877 by Claude Bernard. One of his principal experiments at St. Julien, which he had repeated at various times because he had never been content with the results, had consisted in crushing ripe grapes, sound or decayed, to express and filter therefrom the juice until it was perfectly clear, then to compare in an approximate manner the quantity of alcohol in the liquids after their filtration, and in the same liquids after standing about 48 hours. Bernard found that in this interval the amount of alcohol increased, although the liquid remained clear, and he did not hesitate to draw from this fact conclusions favorable to the existence of the diastase of which we have already spoken.

The experiment of Bernard allowed various sources of error which Pasteur pointed out in the discussion which he made of it. He cites in opposition the results described in the *Études sur la bière*, but he goes farther: he proposes to repeat the same experiments on a much larger scale, in such a way as not to allow any of those conditions of time and place of the experiments of Bernard, which one could invoke in their favor, to come into play. Here, we can let him speak, for he has himself given an account quite at length of this episode, wherein he has painted a very exact portrait of himself, with his ardor in returning to already conquered positions when they were menaced, and that suddenness which he always brought into his decisions when a great question was under consideration.

The day following the posthumous publication of the manuscript of Bernard, Pasteur's plan and program were made: "Without too much care for expense,"<sup>1</sup> he said, "I

<sup>1</sup> Examen critique d'un écrit posthume de Cl. Bernard sur la fermentation, p. 66.

ordered in all haste several hothouses with the intention of transporting them into the Jura, where I possess a vineyard some dozens of square meters in size. There was not a moment to lose. And this is why!

“I have shown, in a chapter of my *Études sur la bière*, that germs of yeast are not yet present on the grape berry in the state of verjuice, which, in the Jura, is at the end of July. We are, I said to myself, at a time of year when, thanks to a delay in growth due to a cold rainy season, the grapes are just in this state of verjuice in the canton of Arbois. By taking this moment to cover some vines with hothouses almost hermetically closed, I would have in October during the grape harvest, vines bearing ripe grapes without any yeasts of wine on the surface. These grapes, being crushed with the precautions necessary not to introduce germs of yeast, will be able neither to ferment nor to make wine. I shall give myself the pleasure of taking them to Paris, of presenting them to the Academy, and of offering some clusters to those of my confrères who may still believe in the spontaneous generation of yeast.

“The fourth of August, 1878, my hothouses were finished and ready to be put up. The work of setting up and of putting in the glass was finished in a few days.

“During and after the installation of the hothouses, I searched with care to see if the germs of yeast were really absent from the clusters in the state of verjuice, as I had found hitherto to be the case. The result was what I expected; in a great number of experiments I determined that the verjuices of the vines in the canton of Arbois and notably those of the vines covered by the hothouses, bore no trace of germs of yeast at the beginning of the month of August, 1878.”

“In the fear that an insufficient sealing of the hothouses would allow the germs to reach the clusters, I

took the precaution, while leaving some of the clusters free, to cover a certain number on each vine with cotton which had been brought to a temperature of about 150°C."

". . . Toward the tenth of October, the grapes in the hothouses were ripe; through the skin of the berry, one could clearly distinguish the seeds, and in taste they were as sweet as the majority of the grapes grown outside; only, under the cotton, the grapes, naturally black, were scarcely colored, rather violaceous than black, and the white grapes had not the golden yellow tint of white grapes exposed to the sun. Nevertheless, I repeat, the maturity of both left nothing to be desired.

"On the tenth of October, I made my first experiment on the grapes of the uncovered clusters and on those covered with the cotton, comparing them with some which had grown outside. The result I may say surpassed my expectation. . . . To-day, after a multitude of trials, I am just where I started, that is to say, it has been impossible for me to obtain *a single time* the alcoholic yeast fermentation from clusters covered with cotton, and as for the uncovered clusters of the same vines I have had only a single case of fermentation, by a yeast which I described a long time ago in the *Bulletin de la Société chimique*, and which has since received from Dr. Reess the name of *Levure apiculée*.

"A comparative experiment naturally suggested itself. When the hothouses were set up we were in the first period, that in which the germs are absent from the stem and the clusters. At the time when the experiments which I have just described took place, from the 10th to the 31st of October, we were, on the contrary, in the period when the germs were present. It was then presumable that if I detached hothouse clusters covered with cotton and exposed them, after removing the cot-

ton, on the branches of vines in the open, these clusters which up to this time could not enter into fermentation after the crushing of their berries, would ferment under the influence of the germs which they could not fail to receive in their new position. This was precisely the result which I obtained."

It is clear that in the presence of these results, nothing was left of the mediocre experiments of Bernard. It was certain that the germs of the yeast were brought periodically to the vine by an external plant, on the nature of which Pasteur could make only some plausible hypotheses, and furthermore, on which we are not yet exactly informed. If I have dwelt so long on this last demonstration of Pasteur, it is not simply to consolidate an already established proof, but to show, by an example which seems to me typical, how Pasteur was able to broaden the problems which he approached.

The problem which he had placed before himself in the preceding experiments was apparently very limited: it was the origin of yeasts. Behold how he enlarged it:

"May I be permitted," he continued immediately after having written the lines which precede, "to enter here into an experimental digression, very worthy of interest? I have said that the clusters of ripe grapes carry on their surface the germs of ferments which produce the wine in the vat and in the casks of the vine grower. Consequently, is it not probable that at the time of the harvest the rains may collect many of these germs and spread them over the soil of the vineyard? Experiment confirms these suppositions. Having deposited very small quantities of earth from a vineyard in a series of tubes which contain the must of grapes sterilized by a preliminary boiling, I have seen this must undergo alcoholic fermentation in many of the tubes of each series. Without injuring the success of the

experiment we may take these samples of earth at a considerable distance from the surface, even from a depth of 10 to 15 centimeters. Still more frequent in this kind of experiment, is the alcoholic fermentation by yeasts of the genus *Mucor*, so abundant in cultivated soil are the spores of these little plants.

“I have had the curiosity to compare the soil of the vineyard and that covered by my hothouses with regard to the presence of the spores of grape yeasts and the spores of *Mucor*. But, although the experiment has been made a great number of times, I have never seen produced in my tubes with the soil from my hothouses, the alcoholic fermentation due to the alcoholic yeasts of the grape; very frequently there appears, on the contrary, the fermentation due to the yeast of the *Mucor*.

“How many reflections these results lead to! . Can we fail to observe that the further we penetrate into the experimental study of germs, the more we see therein unexpected lights and just ideas leading to knowledge of the causes of contagious diseases! Is it not worthy of attention that in this vineyard of Arbois, and this would be true of the millions of hectares of vineyards all over the world, there was not, at the time when I made these experiments which I have just described, a particle of soil, so to speak, which was not capable of provoking the vinous fermentation, and that, on the contrary, the soil of the hothouses of which I have spoken was unable to do this. And why? Because, at a definite moment, I covered this soil with some glass. The death, if I dare to speak thus, of a grape berry which has been thrown on the ground of any vineyard, will be, somehow or other, infallibly accomplished by the yeast parasites of which I speak; but this kind of death will be impossible, on the contrary, in the little corner

of soil which my hothouses cover. These few cubic meters of air, these few square meters of the surface of the soil were there in the midst of a possibly universal contagion, and they withstood it for a period of many months. But of what service would the shelter of the hothouses be in the case of disease and death caused by the *Mucor* parasites? Not the least! Since the parasites of the *saccharomyces* reach the surface of the grapes at a definite period of the year, a shelter, put on in time, was able to keep them free from these germs, as Europe is protected from the cholera and the plague by quarantines. The *Mucor* parasites, on the contrary, being present during the whole year in the soil of our fields and our vineyards, were necessarily under the hothouses when they were put up, like, in some respects, the germs of our common contagious diseases, against which the quarantines opposed to cholera, yellow fever, or the plague are ineffectual.

“Must we not believe, by analogy, that a day will come when preventive measures, of easy application, will arrest these plagues which at one blow desolate and terrify whole populations, as did the yellow fever in its recent invasion of the S n gal and the valley of the Mississippi, or the bubonic plague which has raged on the shores of the Volga.”

These few lines form the introduction to a new life. They show the preoccupations which had just taken possession of Pasteur’s mind and which already completely filled it. They were written in 1879, when the studies of anthrax and of chicken cholera were already begun. They form the connecting link between the old labors and the new, and it is for this reason that I have transcribed them. I should be very much astonished if the reader has not noted their resolute manner of expression and their prophetic tone.







PASTEUR

(From an engraving by Noyes.)

(Courtesy of the Library of the Surgeon General.)

## SEVENTH PART

### STUDIES ON THE ETIOLOGY OF MICROBIAL DISEASES

#### I

#### THE IDEAS ON CONTAGION PRIOR TO 1866

We have reached the period when Pasteur, who had his eyes fixed for a long time upon the promised land of pathology, was going finally to be able to enter it. He was ripe for this work, and provided with the necessary technical outfit to undertake it. His laboratory was at that time the only one in which it was possible to properly handle bacteria and be certain of the purity of a sowing carried through an indefinite series of successive cultures. While elsewhere every one was struggling with nutrient liquids of mediocre composition such as those *mineral solutions of Pasteur* or of *Cohn*, which have played so many tricks with Klebs and those who made use of them, Pasteur had discarded them for a long time, and had adopted the fertile principle of giving to each bacterium the kind of medium adapted to it.

It was following the beautiful researches of Raulin that he had understood the importance of this question. He had reflected for a long time and he called the attention of his pupils frequently to the fact that when cultivated upon its favorite medium, the discovery of which had given Raulin so much trouble, *Aspergillus niger* defends itself unaided and successfully against the intervention of every parasite. While one is obliged to operate protected from the germs of the air and in

flamed flasks, when he wishes to cultivate and keep pure a species the condition for the development of which he knows only imperfectly, *Aspergillus niger* gives admirable cultures, flourishing and pure, in contact with the air, and in liquids and flasks which one has not taken the trouble to sterilize. Consequently, in the presence of every new species, his first care was to try several culture media so as to find that which suited it the best.

Having this principle of culture in the most favorable medium, Pasteur was also the only one who had the ability to add a proper technique. This was due especially, as we have seen, to the efforts of his assistants: Joubert, Chamberland and Roux.

Finally, as a last advantage, Pasteur had that of being 20 years old in the study of microbes and of having more complete notions about them, their needs, their physiology and their morphology, than any of the scientific men of his time. It was because of this that he was able so quickly to catch up with and soon to distance those who had entered before him on this pathway, for at the time when he first took up the study of anthrax in 1876, there had been already several pathogenic microbes discovered, and Koch had just published his famous work on the spore of the anthrax bacteridium.

To appreciate thoroughly the rôle and the part of Pasteur in this great question of pathology, one must know the general state of science and of the scientific mind in 1876.<sup>1</sup> That is not as easy as one might believe it to be, considering that we have to go back only a few years. The ideas which had currency in 1840 and even in 1860 on the subject of contagious diseases are so far removed from our own that they have almost the dis-

<sup>1</sup>One may obtain a very good idea of what it was in Germany by reading Nägeli's *Die niederen Pilze in ihren Beziehungen zu den Infektionskrankheiten und der Gesundheitspflege*, Munich, 1877. *Trs.*

tance of centuries. One finds the same trouble in assimilating them that he would if they were some philosophical work of the middle ages, and therein we see very well what a chimera is the history of scientific ideas. In order to understand the past state of a question, it is necessary to assume an artificial state of mind, to pass the sponge over certain ideas which we believe to be true, putting in their place others which we know to be false, in brief, to change the state of one's brain, and that is impossible.

I know very well that there remain in the books of the period words which are supposed to be the clothing of ideas, and through which one may try to see what they covered. The partisans of the history of science tell us, when it is a question of mathematics or physics or of natural history, that these words have a more precise meaning than when it is a question of philosophy, and they are right. But if they conclude therefrom that the history of science is easy to write, or even possible, they are wrong, for, even in science homonyms are not synonyms 30 years apart. The same tinsels cover very different small rough models. We have just here a striking example of this fact.

For example, the words *contagium vivum* or *animatum* have been current in science for a long time. They have been found in Varro and Columella. Acknowledging that they may still serve to express the ideas of to-day, one has sometimes concluded that these ideas are very old, that only knowledge of the mode of contagion has been perfected with progress of time, and that Pasteur is only the last one come, and the most powerful, of a series of investigators who have labored with the same directive idea.

I have no need to go back very far to demonstrate the inexactness of this point of view. I will confine myself

to the scientific man whom one most willingly cites as the immediate precursor of Pasteur, to Henle who, about 1840, published a sort of theory of disease, the developments of which seem in fact in harmony with our present ideas. For Henle, the evolution of a disease is in all respects comparable to that of a living being. The quantity of *morbid matter* which may produce it in a healthy individual, like the seed of the plant or animal, is out of all weighable proportion to the quantity of effect produced, and to the quantity of *morbid matter* which the diseased individual produces in his turn. An acorn produces an oak, which yields in its turn a multitude of acorns.

So much for a first point of view. Here is a second: Between the time when the *morbid matter* enters into the body, and that in which it is translated into disorders preceding disease, a period intervenes which is well known under the name of *period of incubation*, which is nearly constant for each disease, and differs from one disease to another. How is it possible not to connect it with the duration necessary for the development of the germ and the infection of the tissues? How explain it otherwise than by the doctrine of parasitism? So long as the disease lasts, he who has it must be a source of contagium. When it has ceased, all danger of contagion ceases. This means that the germ is dead and can no longer injure. The same for epidemics. In their appearance, their extension over a territory more or less great, their lingering termination, do they not resemble absolutely the beginning, the middle and the end of a vegetation, and is it not remarkable also that many disinfectants and even remedies should be at the same time active agents of destruction of vegetable or animal life?

Behold, it has been said, an unlettered print of the system of Pasteur, and that which makes still further

for the perspicacity of Henle is that he pointed out the bacteria as among the beings capable of giving infectious germs, and that he thus foresaw and almost enunciated our present day ideas. I reply, you forget a detail which is far from being insignificant. For Henle, the germ of the disease was not something superposed upon the sick person and independent of him, it was something belonging to him, borrowing from him a sort of pathological vitality, and able to transport it elsewhere. The system of Henle is much more in consonance with what one then knew of viruses, of the transmission of smallpox, of vaccine, than with what one had recently learned of the transmission of itch or of muscardine, and we find therein nothing of the new idea brought by Pasteur concerning the living virus, which can be *cultivated* and *modified* outside of the organism.

A physician of La Teste. J. Hameau, had entered upon a better pathway in a paper which, written in 1836, was unfortunately not published until 1847, a long time after the work of Henle. Hameau, contrary to Henle, had taken the itch especially as the point of departure for his deductions and for his system, and all that which is in accord with this premise is correct for he had truly method and logic in his mind. On the contrary he wanders when he takes up the question of miasms, to which he attaches dysentery, erysipelas, and hospital gangrene. For him, there was not in these cases any *contagium vivum*, while there was such for Henle, and that shows us how necessary it is to distrust words, and how much one would have disturbed both Henle and Hameau by placing them in the same camp, under the pretext that they had the same words inscribed upon their banner.

It is not these philosophical speculations which cause science to advance. We must be grateful to all of those from Columella and Varro, by way of Paracelsus, Fra-

castoro and Linnaeus, who have outstripped their epoch by showing with more and more precision the evident analogies between the phenomena of fermentation and of diseases, and who have more or less suspected living organisms in diseases in proportion as they appeared in fermentations. But it is not in these multicolored big lanterns moving about in the night that we are to see the dawn of our present ideas.

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## II

### CAUSES OF THE STERILITY OF THE IDEAS UPON CONTAGION

Such being the case, what one has the right to ask is why these ideas did not attract the attention of contemporaries to a greater extent. Why have systems as suggestive as those of Henle, of Hameau, remained unknown or disdained? We shall here find the secret of their weakness. It is because they were works of the closet and because not being developed from experiment, they did not end in experiment. Systematic and brilliant minds have never been wanting in medicine. When Hameau was writing, Broussais was still alive: the cloud of dust which he had raised, and in the midst of which his disciples were felicitating themselves, was too thick for the vague light of the little physician of La Teste, who explained very well certain known facts, but did not point out new pathways.

In 1840, at the moment of the appearance of the memoir of Henle, the German physicians had, on their side, better excuses than those of to-day for not paying attention to these new ideas. They were too much in opposition to the strong and fertile conceptions that Virchow was introducing at this time into the science.



Without doubt it must be admitted that certain skin diseases like *favus*, *herpes tonsurans*, thrush, and itch could be produced by animals or vegetables. But of what importance were these maladies when placed by the side of the infectious diseases in which one found nothing comparable? Now cellular pathology explained the latter by the famous principles of *heterotopy* and *heterochronia*. Every pathological modification was for it only a physiological transformation displaced in time or place, developing itself in an organ which could not endure it, or at a time when it was abnormal. The secret of the disease was, therefore, in the anatomy of the tissues, which, under this powerful impulse, multiplied its discoveries and took in all, from tumors to viruses, from exostoses to exanthemata, and to the pustules of smallpox or of vaccine.

The idea that there could be in the tissues organisms *come from the exterior* which, by penetrating and developing there, impressed upon them specific modifications, was in disagreement with the general current of anatomical ideas; and yet more with physiological views. At this moment in fact, a pleiad of illustrious scientific men, Helmholtz, Du Bois Reymond, Ludwig and Brücke, began to oppose the ancient conception of the *vital force*, and to explain all physiological phenomena of the living being by forces of the physico-chemical order. It was the same idea that Liebig followed, as we have seen, in the study of fermentations. Into a coterie shining with such names, it is plain with what welcome the idea would be received of the intervention under the form of living and parasitic organisms of this proscribed and everywhere driven out vital force.

And this is precisely why Pasteur who had overthrown the ideas of Liebig respecting fermentations, found it in continuing his work necessary to meet and overthrow

the ideas of Virchow in pathology. If Fate had willed that he should not finish his task, that he should succumb to the *hemiplegia* which attacked him at the time of his studies on silkworms, some other scientific man would have come, a Koch for example, for whom Pasteur would have been a precursor because he would have pointed out the way and left behind him the means of following it. His pathological work was the development and the compliment of his work upon the fermentations. But Pasteur had no precursor in the proper sense of this word, that is to say, he did not develop and extend the ideas of anyone else. He remains the equal of many when he demonstrates the bacterial origin of anthrax or of other diseases. Where he is without equal is when he discovers the attenuation of viruses, and when he introduces into science that fertile notion which allows us to act upon a disease by acting, not upon the sick person, as up to that time one had been in the habit of doing, but upon the pathological bacterium.

What renders his history particularly interesting at this period, is that we can follow the stages of his progress. As we have seen, he had had for a long time the desire to enter into pathology. He was led to it by that secret force of things the elements of which we have just analyzed. He showed himself an eager student of medical works and after having borrowed from them certain words, as we have seen, at the beginning of his studies upon the disease of silkworms, he began to penetrate into things. From this stage his choice was narrowly restricted. He had read and meditated on the works of Jenner upon vaccine, those which Coze and Feltz had just published. But what interested him most of all were the studies which Davaine was pursuing at this time upon the anthrax bacteridium.

## III

## ANTHRAX: POLLENDER, BRAUELL, DELAFOND

The history of this bacteridium was already quite ancient; it began in 1850. It was at this time that Rayer, studying at Chartres the anthrax of horned cattle with the aid of Davaine, had seen it in the form of little rods in the blood of dead animals (Fig. 20), but without comprehending its importance. In 1855, Pollender had seen it again, had noted, like Rayer, the agglutinated condition of the red blood-corpuscles in the anthrax blood, and the considerable number of leucocytes which were observed along with it. In addition, by reactions under the microscope, he had established that the little rods found in this blood were not filaments of fibrin, but behaved on the contrary like vegetation. The principal interest of his communication respecting them centers in the fact that he asked what they signified. Are they the infectious matter itself? Are they only the carriers of this matter? Or, have they nothing to do with it? We should say to-day: Are they the infectious agent, do they convey this agent, or is it necessary to seek it elsewhere? This is the question that Pollender asked himself with much perspicacity, and which it required 30 years to settle.

Science is like a train in the hands of a crew, which, after having gone forward, sometimes goes backward. Scarcely had Pollender well set forth the question than Brauell befogged it by confusing the bacteridia of anthrax, considered up to this moment as sufficiently specific, with the harmless bacteria of putrefaction, which led him quite naturally to discover them in various diseases, and consequently to sever them from anthrax. At most he admits that, in this disease, the harmless

bacteria appear in the blood, before death instead of after death as in other diseases.

The following year he took a new step in the wrong direction. He stated that inoculation with the blood of a horse having anthrax had caused a deadly anthrax in the inoculated animal, although this blood did not



FIG. 20.—Bacteridium of anthrax.

In artificial cultures.

In the blood of a diseased animal.

contain bacteria. Evidently, therefore, these little rods were neither the contagion nor the carrier of the contagion nor even, one might add, the necessary companions of it. Brauell, therefore, undid what Pollender had done. Henceforth the little rods retained only a diagnostic or a prognostic value in certain cases, that is to

say, the animals which showed them in their blood during life had anthrax without question, and were certain to die in the near future, but they might also die of anthrax without containing the bacteridia.

The reaction against these retrograde ideas was set on foot by Delafond, who pointed out the confusion made by Brauell and even by Pollender between the bacteridia of anthrax and the harmless bacteria of putrefaction: because in proportion as the second develop, the first disappear.

Delafond goes further. He seeks to prove the vegetable nature of the anthrax bacteridia by subjecting them to culture experiments. He exposed the anthrax blood in open flasks to the air at a suitable temperature. After 4 or 5 days, the short rods in the blood had increased and doubled or tripled their length, and they quadrupled or quintupled it after 8 or 10 days. This well demonstrated that the bacilli were living. Delafond even tried to push the growth to its completion to see it arrive, as he says, at the *spore* or *seed*. These words *spore* and *seed* had evidently for him not the precise meaning which they have since acquired, but they do honor to his perspicacity, and it is curious to see them appear in connection with bacteridia, in a memoir of 1860.

To sum up then, for those who kept *au courant* with the question, a connection between the bacteridia of Rayer and the development of the disease of anthrax or *sang de rate*, although still obscure, was probable from the proofs and the culture experiments of Delafond. But it is not with such a feeble array of facts that an idea can enter into the domain of science, especially when it finds therein minds prejudiced against it. "What is it worth to us," one might have said at this epoch, "this new etiological doctrine? Is there not something strange about it? Can one imagine the

powerful and colossal life which animates a horse or an ox, threatened and destroyed by this miserable little rod which we can see only under a microscope? This rod appears, moreover, only some hours before death, and when the animal is already very ill. Where is it and what has it been doing earlier? You tell us, you who believe in it, that it does not long survive the animal which it has killed, and dies when the tissues decay. But all animals dead of anthrax decay, for we bury them quickly without making any use of them. And, therefore, how do you explain that there are epidemics of anthrax every year, epidemics which appear in the summer after having disappeared from the country all winter? How do you explain, also, that there are in Beauce *cursed fields*, in Auvergne *dangerous mountains*, where animals from the farm can neither be pastured nor driven, without paying a tribute, more or less great, to the disease? From this is it not evident that the disease is attached to the soil, to the vegetation, and to certain climatic conditions, which have nothing to do with this bacteridium in the blood of diseased animals?

“All that we are able to grant you,” the skeptics might have added, “in the presence of your proofs and of your experiments, is that this bacteridium is an *epiphenomenon*. It sometimes accompanies the virus, or follows it, but it is not the virus itself. The virus of anthrax, like that of smallpox, or of sheeppox, is something which one can handle without seeing it and recognizing it. It exists, since the disease is inoculable, but we do not see it outside of the animal. It is not something independent of the animal but a modality of its being. It is living, it may be granted you, but it borrows its life from the being which carries it, it is nothing outside of the animal, and we recognize it only in transit through living beings.”

All these objections are not wanting in force, and as they favored idleness of mind and invited intellectual repose, they were very much in vogue. To Davaine belongs the honor of beginning again the struggle against them.

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## IV

## DAVAINE

After the discovery of the bacteridium, which Davaine had made in 1850, with Rayer, he had paused for reflection. His was a very keen and discriminating mind. He regarded science from the point of view of medicine. The brief note by Pasteur in 1861 on the butyric ferment, of which we have spoken, had revealed to him the existence of very active microscopic organisms morphologically similar to the anthrax bacillus and capable, by means of their power of fermentation, of producing effects out of proportion to their weight and volume. Consequently, despite its small size, the anthrax bacillus might easily cause the death of a large animal and be guilty of all that was attributed to it. A singular thing which we have difficulty in explaining to-day, is the fact that while no one then refused to admit that a thing as imperceptible as the virus of smallpox could convey the disease and bring death to the individual inoculated with it, because this virus seemed to derive its energy from the creature into which it penetrated, and to change only the modality of its life, all refused to understand that the bacillus, an independent living organism, could by its own activity, triumph over the animal which it invaded.

To Davaine belongs the credit of having seen farther along this line than the men of his generation and of

applying himself to the demonstration of the fact that the bacteridium was the sole *cause* of anthrax. Without entering into the details or the chronology of his memoirs on this subject, it will suffice here to point out the status to which he had brought the question at the time when Pasteur attacked it in so masterly a manner.

It can be said that Davaine had perfectly demonstrated the coexistence of the bacteridium and of the anthrax. This fact of coexistence which is not, however, necessarily to be considered a relation of cause and effect, became known as the result of a long series of observations made on cases of malignant pustule, which is the most common form of anthrax in man, as well as on animals killed by anthrax either naturally, or as a result of artificial infection. This coexistence had been disputed. After Brauell, Signol, Leplat and Jaillard, Bouley and Sanson had published observations or experiments in which anthrax seemed to be present and the bacteridium absent. But Davaine had replied to this by showing that these scientists either had failed to recognize the bacteridium or else had called something anthrax which was not anthrax.

Leplat and Jaillard, for example, imparted a deadly malady to rabbits by inoculating them with putrid blood from an anthrax victim, or in default of that, with bacteria of putrefaction, and did not find bacteria in the blood of the dead animals. "Nothing is less astonishing," replied Davaine, "your malady, and also that of Signol, is not anthrax. It differs from the latter in its shorter incubation period, because it is accompanied neither by the agglutination of the blood-corpuscles nor the congestion of the spleen, the most constant and characteristic symptoms of anthrax, and because it kills birds, on which the bacteridium has no effect. Do not be surprised, therefore, that in this new



malady there are no bacteridia in the blood." The argument was solid, well supported by facts and entirely worthy of the one who produced it.

"This is not all," continued Davaine, "the bacteridium is not simply the inseparable companion of the disease. It is the cause of it, and the only cause. The proof is this: As long as the bacteridium is not present in the blood, the latter is not infectious, and it becomes so when the organism enters it. If from the sick animal, some hours before its death, you take blood with which you inoculate another animal you will not impart to the latter the disease. If you inoculate it with blood as soon as the microscope shows bacteridia in it, the inoculated animal will die. If you wait to make the inoculation until the bacteridia have disappeared under the influence of putrefaction, you would then possibly obtain the malady of Leplat and Jaillard but not anthrax.

"You may say, it is true, that in this experiment, the blood before, during, and after the appearance of the bacteridium is not the same blood, or at least may differ in other ways than that which the microscope reveals in the presence or absence of bacteridia. But here is another argument. Take a pregnant animal, give it anthrax and when it is dead make inoculations with the blood; it is infectious; at the same time make inoculations with the blood of the foetus; it is not infectious. This blood is, nevertheless, the direct emanation from the blood of the mother from which it receives through the placenta all the soluble elements. The placenta, acting as a filter, keeps out only the bacteridia and because of their absence the blood of the foetus is incapable of transmitting anthrax.

"Does not that seem to you proof? Here is another experiment: Filter blood from an anthrax victim through a porous earthen filter, as Klebs and Tiegel have done.

No solids pass through the filter. The serum passes through and it is not infectious. The cause of the malady is, therefore, not soluble in the serum. It remains on the surface of the filter where there are only red corpuscles, white corpuscles and bacteria. Choose the cause among these three, but choose!"

Davaine was not only ambitious to demonstrate that the bacteridium was the cause and the only cause of the development of anthrax: he wished also to explain by its aid the etiology of the disease, that is to say, the different conditions governing its natural appearance and its endemic or epidemic character. In this direction he was less successful. He had observed, as we have just said, that putrefaction rendered the blood incapable of transmitting anthrax. He was obliged, therefore, to give up seeing in the blood and tissues of an animal buried as a victim of anthrax the cause of the revival of the disease from one year to another, in the same region or pasture. He observed, nevertheless, that blood rapidly dried preserved its virulence for a long time. Now, said he, this rapid desiccation must often occur in countries where anthrax is prevalent; when animals are slaughtered for the sake of the skins, pools or drops of blood remain on the ground, on the litter, on the walls, and these dry rapidly and preserve their germs. As for the infection of other animals, Davaine attributed it to flies some of which by sucking, and others simply by means of their feet, are the agents of infection among animals in stables or the open field, and he supported all these opinions by well carried out experiments.

There were grave objections to this etiology. If it is the fly which disseminates the virus, it was said, why does it sometimes respect so carefully the boundaries of a field or an estate? There are in Beauce and in Auvergne dangerous fields or meadows; the adjoining

meadows are not so; why do not the flies pass from one to the other? And furthermore, if they are the agents of transmission all the cases of anthrax in animals ought to begin with a subcutaneous tumor or a lesion of the mucous membrane, similar to the malignant pustule in man, the origin of which is always external.

But these cases of external anthrax are very rare among the domestic animals. It was necessary, therefore, to search for some other explanation. But what? No one knew. In the meantime, as long as the bacteridium did not explain or explained so badly the etiology of the disease, the partisans of the theory of spontaneous anthrax had a good chance, and the opinion of the investigators was still wavering when the work of Koch appeared. This dissipated many of the obscurities and silenced some of the objections.

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V

KOCH: THE SPORE OF ANTHRAX

It was in reality this work which introduced into the question a very important idea, that of the spore, which plays so great a rôle in our ideas of to-day, but which at that time, was unknown or at least abandoned. Pasteur had observed, in 1863, the formation of spores in the butyric vibrios. But he had not foreseen their rôle nor did he know their exact significance. In 1869 he had found them in the vibrios of the *flacherie* of the silkworm and, this time, he had proved that these spores, these cysts, as he called them, had a resistance greater than that of the rods, and could endure a long drying. By means of these cysts he had explained the persistence of the epidemics of *flacherie* in different regions.

After Pasteur, Cohn had studied the mode of formation and the resistance of these spores in *Bacillus subtilis*, and had put forth the hypothesis that the bacteria of anthrax possibly behaved like this bacillus. But none of these precedents detract in the least from the merit of Koch: it was he who showed the rôle of the spore in the etiology of anthrax, and he did it in a way truly marvellous for its simplicity.

If one places in the thermostat or even leaves exposed to summer heat a drop of fresh beef-blood serum or of the aqueous humor of the eye, sown with a very small fragment of fresh spleen from a mouse affected with anthrax, a microscopical examination at the end of 15 to 18 hours shows the following appearances: in the center of the slide which covers the preparation, where the air cannot penetrate easily, the bacilli are in their original state and have not elongated. Half way, from the edges of the cover-glass the bacilli are longer, twisted and bent and so much the more elongated as they are nearer the margin. Certain ones, those which are most in contact with the outer air, contain typical spores, sometimes arranged regularly in the filament like beads (Fig. 20, left side). Ultimately these free themselves from the envelope in which they are formed. They are then disseminated through the liquid like an amorphous powder. But this dust is living, for, if transferred to a new drop of serum, these spores produce at the end of 3 or 4 hours new bacilli, capable, like the first, of causing the death of the animal inoculated with them. There is then no diminution of virulence in passing through the spore state.

We see that Koch, passing over and beyond Davaine, who had not thought of it, was not satisfied to repeat Delafond's cultural experiments. He succeeded in the first attempt in doing that which Delafond had tried

to do in vain—in forcing the rods of the anthrax to produce spores. Furthermore he gave to this spore an important place, which it has not since lost, in the etiology of the disease. He did this by showing that it always forms in the blood and tissues of an animal dead of anthrax, if the temperature is suitable and there is sufficient oxygen.

These two conditions are necessary. Below 18°C. spores are not formed; at 30°C. they occur at the end of 30 hours; at 35°C., in 20 hours. The rapidity with which spores are formed is, therefore, directly proportional to the amount of heat. Oxygen is also indispensable. Anthrax blood, if deprived of this gas, ceased to be virulent in 24 hours without putrefaction. When the blood is allowed to putrefy, the virulence also disappears if putrefaction exhausts the oxygen quickly enough so that the spores have not time to form at the temperature to which they are exposed. If the spores have already formed, putrefaction does not kill them or prevent them from developing ultimately on the same field or in the same region if circumstances are favorable. All the contradictory results of previous investigators on the duration of the virulence of the blood or of diseased organs, some saying that it could persist, others that it was lost immediately, were at once explained. The persistence of the disease and its return in an infected country was also explained, and in an entirely natural way. It was the spore which was the agent of preservation, which persisted where the conditions of temperature and of aëration had permitted it to form, and where it always held itself in readiness to make new victims.

Koch was not satisfied in thus broadly explaining the etiology of the disease. He studied the mode of transmission, proved that the symptoms of natural

infection revealed infection through the food, and actually demonstrated that the small animals of the laboratory could contract anthrax when the anthrax bacilli or the spores were mixed with their food. For want of resources he could not make the same experiments on the large domestic animals, and regarding them he left the question an open one. He also left undecided the problem of infection by respiration and through the lungs. But science had nevertheless made a great stride when, with the discovery of the spore and its power of resistance, there disappeared one of the great objections which the etiological conception of Davaine had raised.

Nevertheless, the victory still remained indecisive, for a new adversary had arisen. To the affirmation of Koch, P. Bert had replied in 1887 by an experiment in which by exposing anthrax blood to the action of compressed oxygen, he killed or at least believed he killed the bacteria. Inoculation of this blood thus robbed of the parasite produced the disease and death, without the reappearance of the bacteria. Therefore, he concluded, the bacteria are neither the cause nor the necessary effect of the anthrax disease. It was reverting, with new arguments, to the idea of Brauell which we discussed in the beginning of this short history.

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## VI

### OBJECTIONS TO THE NEW DOCTRINE

From what standpoint could a man, as unfamiliar with this class of studies as Pasteur, regard the facts which precede, studying them with his characteristic vigor? From what standpoint also ought the medical

men of the time to have regarded these new ideas, obliged as they were to reconcile their desire for the progress of science with scholastic traditions and the hatred of innovation, so native to the practitioner. Objections occurred naturally. These remained vague to medical men because for the most part they did not have the laboratory spirit, but they were formulated more clearly in the mind of Pasteur, and behold the result!

In the first place anthrax appeared clearly to be a contagious, inoculable disease due to *something* which taken in an infinitesimal quantity from a diseased animal could produce the disease or kill a sound animal after a period of incubation which was evidently a period of development and of invasion of the organism. But what was this something? Was it the anthrax bacteridium, as Delafond, Davaine and Koch said? Was it a virus, as tradition would have it—the tradition created by what was known of smallpox, vaccine, and sheeppox, and even by what was supposed to be known about glanders?

The question does not seem very important to us, who have made a choice, and who, furthermore, with our knowledge, and without being misunderstood, are able to give the name of virus to the anthrax bacteridium itself. But 20 years ago the domain of viruses and that of parasites remained separate. M. Chauveau, who was one of the first to make a remarkable study along this line, defined virulent diseases as contagious diseases which were neither caused nor transmitted by a parasite.

This distinction not only seemed well founded, but determined the direction which research was to take. A virus could be cultivated only within the animal organism adapted to it. It could enter it in various ways and produce in it different manifestations according

to the point of entry, but it did not on that account change its nature, and its *entity*, its fundamental unity in the midst of the different phases of the disease which it produced, was the foundation of the doctrine. Without doubt variations in strength, in virulence, had been observed when a virus was transmitted from one species to another, but this had been observed also and even to a greater degree in the same species; epidemics of smallpox were more or less benign; smallpox produced by inoculation was ordinarily less dangerous than that which had furnished the material for the inoculation. All of these variations in the severity of the disease or of the epidemic seemed beyond the reach of experimentation and were attributed to external factors, cold, heat, or meteorological conditions. Such is the state to which one was reduced by the impossibility of observing the virus outside of a living creature.

If, on the contrary, the bacteridium is a ferment, a parasite, the aspect of the question is changed. We can cultivate the bacillus outside of the organism, study its properties, learn its physiology, and compare its physiological with its pathological rôle to discover what effect its normal functions have on the normal functions of the animal it invades. Disease resulting thus from the physiological conflict between two organisms which can be studied separately, its study took a new direction. It is very clear that Pasteur was not thinking at this time of variations in virulence among bacteria, nor of vaccinations. But his was an intellect so keen that I would not affirm that this idea was not in the background of his mind and I could cite as an argument the eagerness with which he fell upon the first explicable fact in this class of ideas. We shall see him at this presently. In the first place, the important question to be solved seemed to him to be this: is the essential agent of anthrax



the bacteridium, or the virus which accompanies this bacteridium?

Viewed from this standpoint the results of Davaine and even those of Koch left room for hesitation and doubt. When one made inoculations, as Davaine did, with anthrax blood, he inoculated along with the bacteria all the substances accompanying them in the blood, and among these there might be a substance in the nature of a virus, developing along with the bacteria in the inoculated animal and escaping observation because one could not distinguish the virus microscopically from granulations of the organic liquids. The bacteridium, which can be seen and distinguished, seems, therefore, to develop alone and to be the exclusive cause of the malady, when it is possible, that it is only an epiphenomenon as they say in the medical school

The experiments dealing with the natural filtration of the blood through the placenta and of artificial filtration through a porous wall, which Davaine presented as arguments in favor of the rôle of causal agent belonging exclusively to the bacteridium, demonstrated only that this active rôle was not vested in the *soluble* elements. We know, since Chauveau's time, that a virus is a solid organized body which cannot pass through the placenta or porous plates and which, remaining on the surface of the filter with the bacteridium, may be inoculated with it.

Koch had made more convincing experiments along this line. He sowed in a drop of serum a tiny drop of blood or bit of tissue from an anthrax victim, and left the culture to grow. Then, from this first culture, he had inoculated a new drop and thus made 8 successive cultures, the last of which was capable of producing anthrax in a healthy animal. But there again, there was room for a doubt. There was no certainty that the

virus was not carried by the blood into the first drop, thence transferred diluted to the second, third, etc., and was still present in sufficient quantity in the last drop to produce the effect attributed to the bacteridium. Chauveau's experiments had just shown that viruses could undergo great dilution, as much as 1/150 for the vaccine, 1/500 for glanders, which was ranked then, as we have said, with smallpox and cowpox. These cultures of Koch's were neither numerous enough nor made in sufficiently large volumes of liquid to eliminate the influence of the virus from the dilution. Add to that the results of P. Bert, which were still perplexing to the partisans of the new doctrines.

All these objections appear to us to-day as mere hair-splitting. It is certain that if any one should bring to us now, for any disease whatsoever, such a collection of proofs as those which Davaine and Koch furnished for anthrax, no one would have the least doubt of their significance. Why? Because the ideas of men of research and of the public have orientated in this direction. The weather-vane has turned; but this vane turned only with much difficulty and much squeaking. Davaine and Koch had blown at it in vain with all the power of their lungs, they had succeeded in stirring it but not in changing its position. It was Pasteur who overcame all resistance by putting to rout everything which served as a pretext for immobility and inaction.

This definite orientation of mind and effort was the more urgent because for 10 years science had struggled with the difficulties and obscurities of the subject and multiplied its labors and discoveries without seeing light burst forth from any side. The ideas of Pasteur on fermentation did not create a stir solely in the study of anthrax; the preoccupation with the rôle of bacteria in pathology was general. Klebs had found

organisms in purulent nephritis in 1865; Rindfleisch in pyemia in 1866; von Recklinghausen and Waldeyer in metastatic abscesses in 1865. In 1872 Klebs had shown how, starting from a wound, bacteria could penetrate the lymphatics or the veins by means of the interstices of the connective tissue, and from there infect the thrombi of the blood vessels or produce abscesses. Then came the discovery of bacteria in erysipelas, hospital gangrene, puerperal fever, diphtheria and other diseases.

But on all these points there was still more legitimate cause for doubt than in the case of anthrax, and far from corroborating each other these different discoveries succeeded in being almost contradictory. Instead of bringing order, they seemed to produce confusion. For example, contrary to what appeared logical, pus of the same nature and origin contained very different organisms and, on the contrary, forms almost indistinguishable occurred in very distinct diseases such as smallpox, diphtheria and cholera. In a general way the organisms discovered in these diseases bore a striking resemblance to each other and could scarcely be said to have any special physiognomy, except the anthrax bacteridium, on account of its size and because it was found in the blood, and the spirillum of recurrent fever, discovered in 1873 by Obermeier, which also passes into the blood when the fever is at its height, and the spiral form of which serves to distinguish it. All the other organisms were alike in form, size and properties, and this formed an argument of which those who resisted the contagion of the new ideas were not slow to avail themselves.

Finally, to complete the perplexity of investigators, bacteria were not found in some diseases which were clearly of a contagious nature. After having set up

the virus in opposition to the microbe these persons now asked: Why are not bacteria present in all virulent diseases? However, an answer to this question was just beginning to be found in a simple perfection of technique which had demonstrated the presence of organisms where their existence was suspected, but where they had not been seen.

Their discovery was easy in anthrax, where they pass into the blood, even before death. It is more difficult, even in anthrax, to trace them in the organs of the body. There were only very imperfect methods for doing that: the treatment of the tissue with potash, as Davaine advised, or with acetic acid, as in von Recklinghausen's method. We cannot be too grateful to C. Weigert for the great service he rendered in 1875 by teaching us how to stain bacteria with basic anilin colors, and thus to make them visible in the tissues. Two years later, Koch achieved a new advance in technique by teaching us to study unstained structures microscopically with a very subdued light and stained objects with a flood of light [structure-picture *vs.* color-picture].

We see, from this brief exposition, that the science was mature, and that, moreover, it was thoroughly equipped for new discoveries. What did it lack? Faith, the conviction that it would not be deceived on entering these new paths, and that there were genuine bacterial diseases. It is this demonstration that Pasteur gave.

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## VII

### PASTEUR: THE BACTERIDIUM IS THE SOLE CAUSE OF ANTHRAX

To this question: Is it a virus? Is it a microbe? Pasteur was happily in a better position to reply than any one would have been in 1877. From his *Études sur*

*la bière*, and his contests with his opponents, he came out well equipped, with a perfected technique, and a knowledge both of bacterial species and of how to grow them. To solve all these problems he could draw only from his own depths, and this he showed at once.

Old observations and experiments had taught him that the blood of a sound animal, taken as it circulates in the veins and exposed to air which is free from germs, does not putrefy at the highest temperatures, nor give birth to any organism. It seemed to him probable, therefore, for he knew nothing then of the cultural experiments of Delafond and of Koch, that the blood of an animal infected with anthrax, if sown in a suitable medium, would stock it solely with anthrax bacilli which he could then keep pure for an indefinite time in successive cultures, as he had done with yeast and other ferments.

Experiment proved it to be so, and showed that this bacteridium multiplies abundantly in urine made neutral or slightly alkaline. From that time, the problem was solved. Let us take a series of cultures of this bacteridium transferring each time one drop from the preceding culture into 50 cc. of fresh urine. The first dilution is 1/1000, the second 1/1,000,000, the third 1/1,000,000,000, etc. After ten cultures it falls to such a figure that the original drop of blood which furnished the first sowing, has been, so to speak, drowned in an ocean. Everything that it carried with it, to which we might be tempted to attribute a rôle in the production of anthrax—red corpuscles, white corpuscles, granules of all sorts—are either destroyed by the change of medium or are widely disseminated in this ocean and are lost there. Only the bacteridium has escaped the dilution because it has multiplied in each of the cultures. But a drop from the last culture kills a rabbit or guinea

pig as surely as a drop of anthrax blood. It is, therefore, to the bacteridium that the virulence belongs. Behold a conclusion of the first rank firmly established, avoiding the objection which could be made to the corresponding conclusion of Koch, because Pasteur, at this time, knew how to make with certainty an indefinite series of cultures, while Koch learned to do this only later. Such is the advantage of technique.

This first step taken, we can ask ourselves how the bacteridium acts. Does it secrete a soluble poison which spreads about it in the liquid, as it undoubtedly spreads in the tissues of an attacked animal to produce the disease and kill it? No, for the liquid of the culture, filtered through a porous membrane and injected in any desired quantity into a rabbit, barely makes it sick. This time it was Davaine's experiment but carried on under convincing conditions because the experiment was not with a complex liquid like the blood, but with an artificial culture of the bacteridia.

Finally there remains the hypothesis that the bacteridium itself produces a virus in the form of living granules which it disseminates in the liquid or in the tissues, and which alone is the active agent. This hypothesis accepts the bacteridium: its only object is to connect the bacteria with the virus, whereas the actual current of events is, on the contrary, to connect the virus with the bacteria. But it matters not! To this objection, Pasteur and Joubert responded that nothing suggestive of virulent granules can be seen in the liquid of a bacterial culture even when examined with the highest magnifications. There are only well-defined filaments, floating in the midst of a perfectly clear liquid. We have the right to consider this reply as insufficient, since nothing is to be seen in the yellow serosity of some pustules of sheeppox, yet we know that it is virulent.

Strictly speaking, it is entirely possible that a virus should exist in the sense formerly attributed to this word, produced by the bacteridium and accompanying it in all its cultures. But this is the essential thing, that it is not produced independently of the organism, and that, consequently, whatever the mechanism of its action, the bacteridium is the sole cause of anthrax.

This is the demonstration which the note of April 30, 1877,<sup>1</sup> gave with a clearness and conciseness truly marvelous. It was said at the time and has been repeated since, that it was unnecessary, and that the proof which it set forth had already been made and accepted by many scientific men. Yes, but it was not accepted by all, and those who did accept it were incapable of convincing others. Some of us had faith, nobody had assurance or certainty. Henceforth, there was a sure beginning of things, and a method of work: one could go ahead, and Pasteur made haste to reach the goal before the others.

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## VIII

### CONFLICT OF THE MICROBE WITH THE ORGANISM

In order to comprehend thoroughly the history of his efforts from this time on and not to be too much impressed with their seemingly disconnected character, we must recall the fact that Pasteur was neither a physician nor a veterinary surgeon, and that the history of any disease, *as a disease*, did not interest him deeply. That which he studied in the anthrax bacteridium was not the anthrax, but the mode of reaction of the microbe

<sup>1</sup> Pasteur et Joubert, Charbon et septicémie, Comptes rendus de l'Académie des Sciences, 1877.

toward the organism in which it developed. Every bacterial cell able to become pathogenic in any way or by any means whatsoever, and thus to throw light on the mechanism of the struggle with the cells of the host organism, was welcome in his laboratory.

It was for this reason that he sometimes passed so easily and so rapidly from one organism to another. It was also the reason why he was so indifferent to their morphology. A clever and positive micrographer who came to him one day and told him in very cautious language that a certain microbe which he had taken for a coccus was in reality a very small bacillus, was very much astonished to hear him reply: "If you only knew how little difference that makes to me." Perhaps he carried this disregard of anatomical detail a little too far. But his rule was to attack at once the most important things and to neglect trifles.

With his prodigious insight, he had divined at once that, for the solving of these problems, he had a weapon which none of his predecessors had possessed. He was able, as we have said, to study, in pure culture, the physiological properties of the bacteridium, or of any other microbe, and to compare them in their pathological reaction. In other words, he could establish the etiology of the disease, not only by establishing more firmly than had hitherto been done a relation of cause and effect between the microbe and the disease, but by connecting each one of the symptoms of the disease with the reaction of the physiology of the micro-organism on that of the tissues. This was the new program, which he pursued instinctively, perhaps without deliberate intention, but led by his habits of mind and the trend of affairs in his laboratory. At once, he reaped a harvest of discoveries.

For example, the anthrax bacteridium is aërobic,



as Koch had seen, and must have contact with oxygen in order to live. Therefore, as soon as the bacteria reach the blood they struggle with the red corpuscles for the possession of this gas, and, consequently, the latter are asphyxiated. Thus, clearly, originates the black color of the blood and viscera at the moment of death, which is one of the most marked characteristics of anthrax.

These corpuscles of anthrax blood are, furthermore, agglutinated and massed together. Why? Because of a secretion of the bacteria. Anthrax serum filtered and mixed with fresh normal blood agglutinates the corpuscles as much and even more than occurs naturally in the disease, due, without doubt, to a diastase which the bacteria have secreted in the culture medium. Here we have the first example introduced into science of a bacterial secretion producing one of the symptoms of a disease.

The second, still more striking, was taken some months later from the history of chicken cholera. One of the most curious symptoms of this disease is the unconquerable somnolency which overtakes the diseased fowls. But one can produce a somnolence entirely similar though less profound by inoculating a healthy animal with a filtered culture of the microbe of chicken cholera. The filtered liquid is free from the microbe but contains substances secreted by it, which we call to-day its *toxines*, and this word alone is sufficient to recall all that has sprung with time from this fundamental observation of Pasteur concerning which we have just spoken.

We are not yet done with this note of the 16th of July, 1877, from which we have derived the preceding facts. There are some species of animals which are refractory to anthrax. Such are the birds. Nevertheless the blood

of a bird, drawn from the animal, is an excellent culture medium for the bacteridium. Why does it resist infection in the animal? Because "the living blood in full circulation is filled with an infinite number of corpuscles which in order to live and perform their physiological function, need free oxygen: it might be said that the blood corpuscles are obligate aërobes. When, therefore, the anthrax bacteridium, enters normal blood, it meets there an enormous number of organic individualities ready, figuratively speaking, for what one sometimes calls the struggle for existence, ready, in other words, to seize for their own use the oxygen necessary for the existence of the bacteridium."<sup>1</sup>

We see developed here the formula and the ideas of Darwin, but in a singularly precise form. What could be more vague than the phrase "struggle for existence?" But "struggle for oxygen," that opens the way to experimentation, and Pasteur begins at once.

Some common bacteria sown with the anthrax bacteridium, in neutral or alkaline urine, prevent its developing because they take possession of the ground more rapidly and exhaust the oxygen. They can, in the same way, arrest its development in an animal. "It is possible to inject great quantities of the anthrax bacteridium into an animal without its contracting the disease, if some of these common bacteria have been present in the culture used." Here we have the first example of *bacteriotherapy*, to which Cantani returned later, and which has not spoken its last word.

The interpretation of these facts has changed, and we know now that it is less simple [than it seemed at that time] but the idea of the struggle for existence was nevertheless then introduced into pathology, in the domain of cellular antagonism: and it has remained there.

<sup>1</sup> Comptes rendus de l'Académie des Sciences, 16 juillet, 1877.

## IX

## THE SEPTIC VIBRIO

This idea also shed a light over the past. We have seen that MM. Leplat and Jaillard had contested the interpretations of Davaine by showing that an animal inoculated with putrid anthrax blood died quickly with symptoms analogous to those of anthrax, but without having bacteria in the blood, a proof to them that the presence of the bacteridium in anthrax was only an epiphenomenon. To that, Davaine had replied that the disease produced by Leplat and Jaillard was not anthrax, but differed from it in the length of the incubation period and in many other ways. He was right, but exacting minds, and it is always necessary that there should be such in science, were justified in finding his reasons insufficient. It might be, after all, that the disease produced by Leplat and Jaillard was the true anthrax and Davaine's was an anthrax modified by the presence of the bacteridium. The intervention of this microbe might well change the symptoms, modify the evolution of the disease, and permit it to attack other species of animals.

How was one to meet this objection, which was like viewing the same facts through opposite ends of the lorgnette? There would have been one way, viz., to discover the cause of Leplat and Jaillard's disease. But in his attempt to do this Davaine was shipwrecked, in spite of his efforts. He had found the anthrax bacillus in the blood: it was in the blood that he searched obstinately for the second disease but he found nothing there. If it had occurred to him to examine the tissues he might have found myriads of the organisms which he sought. The abdominal serosity in particular is full

of them, it is almost a pure culture of the microbe (Fig. 21), while in the blood the rods are rare, more elongated and difficult to find in the midst of the corpuscles; furthermore, they enter the blood late in the course of the disease and Davaine had not seen them there. Thus



FIG. 21.—The septic vibrio in the abdominal serosity and in the blood. In the serosity the forms are variable. In the blood they are long filaments, infrequent and hard to see in the midst of the corpuscles.

it is that one can just fail of making the most beautiful discovery.

Pasteur, for whom everything was a pretext for microscopical study, did not allow this opportunity to escape, and threw himself with his customary ardour into the study of this new microbe. There also, a harvest of facts awaited him.

This one, immediately: This organism is a common one. The disease which it causes is identical with that which Signol had produced, two years before, by inoculating with blood taken from the deep-lying veins of a healthy animal, asphyxiated 15 or 20 hours. In this case the bacteria reach the blood by way of the intestinal canal which often contains millions of them, but where they are harmless. Only after death do they pass the barrier which this canal opposes to them, and reach the organs and the blood.

It was the same bacterium that was present in Leplat and Jaillard's putrid anthrax blood: as the disease which it causes develops more rapidly than anthrax, it gets the better of the latter in the animals which have been inoculated with this blood and we see it alone. Davaine, therefore, was right. The animals which Leplat and Jaillard inoculated did not die of anthrax, and it was left for Pasteur to tell what killed them.

Finally, it was probably this same organism which caused the illusion of P. Bert. The blood in which he believed that he had killed the bacteridia with oxygen, and which gave anthrax without microbes when inoculated, very probably contained Signol's organism protected by its spore stage against the action of oxygen, and bringing to the inoculated animal the disease of which it is the agent.<sup>1</sup>

Thus disappeared with one wave of the wand the greatest of the objections to the new etiology of anthrax. But this was not all. Pasteur made haste to subject the new bacterium, which he has made famous under the name of *septic vibrio*, to that physiological study

<sup>1</sup> This disease, common to man and various domestic animals, is known variously to-day as gangrenous septicemia, malignant œdema, traumatic gangrene, gaseous gangrene, etc. It is believed to be due to various distinct anaërobes called *Vibrion septicque*, *Bacillus œdematous*, *Bacillus welchii*, *Bacillus egens*, etc. *Trs.*

which had been so successful with the anthrax bacteridium. He saw at once that he could cultivate it only in the absence of air, as it was an obligate anaërobie.

Therefore, he concluded, with the assurance that long practice had given to him, it is a ferment, and, in fact, in culture media it liberates gas, forms carbonic acid, hydrogen and a small amount of hydrogen sulphide which imparts an odor to the mixture. How is it that this fact was not deduced at once from that other fact, namely that when a post-mortem is made on an animal which has died of septicemia, we find tympanites, gas pockets in the cellular tissue of the groin or of the axilla, and frothy bubbles in the serosity which flows from all points in the body when an opening is made. The animal exhales a characteristic odor toward the end of its life. Its parasites, driven out it may be by this production of hydrogen sulphide, leave the skin to take refuge at the extremity of its hairs. In short, septicemia may be termed a putrefaction of the living organism.

When the anaërobic character of the septic vibrio was once discovered, a series of logical deductions at once presented themselves.

“When a liquid containing the septic vibrio is exposed to pure air, the bacteria ought to be killed and all virulence destroyed. That is what happens. When some drops of septic serosity are spread out in a very thin layer in a tube placed horizontally, in less than half a day the liquid becomes absolutely harmless, even though in the first place it was so virulent that inoculation with the very smallest fraction of a drop would produce death.

“Furthermore, all the vibrios which occur in profusion in the liquid in the form of motile filaments, are destroyed and disappear. We find after this exposure

to the air only fine amorphous granules, which cannot be cultivated and which will not communicate any disease whatsoever. One might say that the air burns up the vibrios.

“If it is terrifying to think that life is at the mercy of the multiplication of these infinitely small organisms, it is, on the other hand, consoling to hope that science will not always remain powerless before such enemies, since having barely begun the study of them, she has taught us, for example, that simple contact with the air is sometimes sufficient to destroy them.”<sup>1</sup>

The progress we have just made seems perplexing in the light of what we already know. How can septicemia exist if air destroys the vibrios? How can the blood, kept in contact with the air, become or remain septic? How did Leplat and Jaillard, who had no idea of anaërobic life and its demands, obtain, almost at once, septicemia in the animals they inoculated? The reason for this is that all we have said is true for vibrios in course of development but it does not hold good for the spores. The latter do not form in contact with air. They are not produced in the serosity spread out in a thin layer such as that just described. But place the same quantity of serosity in a tube of small diameter which we keep upright, and allow the oxygen to act on it in the same way and all will be changed. The vibrios on the surface die by absorbing oxygen and thus protect those in the depths, which have time to form spores. The latter, once formed, have nothing to fear from the air, and the liquid which the oxygen had rendered harmless in the first instance, here remains virulent, because instead of being in a horizontal tube it is in a vertical one.

<sup>1</sup> La Théorie des germes et ses applications à la Médecine et à la Chirurgie. Lecture faite à l'Acad. de Médecine, le 28 avril, 1878.

Pasteur who believed he could never accumulate too much proof in support of his opinion, was here not unmindful of the fact that the animate cause of certain virulent diseases was still contested. He had a beautiful argument to add to those which he had already given on anthrax. He made it instantly in the same shrewd way that he made an ingenious analysis.

“We should search,” he says, “for proof that apart from our vibrio there is no independent virulence peculiar to liquids or solids, that, in short, the vibrio is not simply an epiphenomenon of the disease of which it is the obligate associate” (*l. c.*). Here are two liquids which are identical in the beginning, exposed to air for the same length of time. One remains virulent, the other does not.

They continued originally and both still contain two kinds of substances—solids and fluids. To which does the virulence belong? It is evident that the substances in solution have remained the same in both cases. It is not possible to imagine any action produced on them by the air which would not be alike in both tubes. Only the solids, and there are none except the vibrios, have undergone a change, being converted into resistant spores in one case, and harmless granules in the other. It is, therefore, to these alone that the virulence must be attributed.

We have not finished. We have just demonstrated that the spore is the resistant aërobic form of the anaërobic vibrio. How does it return to the vibrio stage? This is equivalent to asking, since the spore-form occurs everywhere, under what circumstances does it again become dangerous? We shall soon see with what brilliancy Pasteur answers this question.



## X

## A COMMON MICROBE MAY BE PATHOGENIC

The septic vibrio, we have said, occurs everywhere. Almost always there are billions of them in the intestinal canal of all animals. We invariably find them in the soil, and, from studies on the etiology of anthrax, which we shall meet again shortly, Pasteur was convinced that the chances were very great that a guinea pig or a rabbit inoculated with drainage water from any soil whatsoever would die of septicemia.<sup>1</sup>

Here, therefore, we have a very common organism, which we discover to be very dangerous and capable of causing a deadly malady when it enters the tissues through a wound. Why this penetration of the tissues does not occur more often and why the malady induced thereby is not inscribed on the list of prevalent diseases was an embarrassing question, and one with which the partisans of the theory of the spontaneous generation of disease should have triumphed. "You see clearly," they might have said, "that something more than the microbe is needed to make us ill, since in this case we so often find the organism and so rarely the disease." Pasteur knew well that he laid himself open to attack, since this theory would not be easily accepted, that a common organism could become pathogenic under certain conditions and at certain times, and it was for this reason that at the end of his Note to the Academy of Medicine he gathered together examples and proofs of this fact. This Note, which seems a little disconnected, is unified only when it is regarded in this light.

<sup>1</sup> Examinations made during the late German war, in which gas gangrene very commonly followed neglected wounds, indicate that this organism or one acting like it occurs in practically every gram of soil in Northern France and Belgium. *Trs.*

His method was as follows: to demonstrate for the septic vibrio that the return of the spore to activity and to virulence does not depend on the obscure questions of *vital force* or *vital resistance*, which medicine invokes so readily, but that it is simply a question of the presence or absence of oxygen; then, when he had thus smoothed the way, to marshal together and launch, somewhat pell-mell, other analogous facts regarding the ability of water- and soil microbes to become pathogenic. Now that we know his plan of campaign let us see how he carried it out.

In the first place let us ask if "the germ corpuscles of the septic vibrio, although formed in a vacuum or in pure carbonic acid gas, would not need, in order to become active, a small quantity of oxygen. Physiology does not know to-day of any case in which germination is possible in the absence of air.<sup>1</sup> So be it! nevertheless, experiment has shown that the germs of the septic vibrio are absolutely inactive in contact with oxygen, whatever may be the proportion of this gas; but this is always on condition that there is a certain relation between the volume of air and the number of germs, for the first germinations, using up the air which is in solution, may serve as a protection for the remaining germs, and it is thus that, actually, the septic vibrio may propagate itself even in the presence of small quantities of air, but not if much air is present."

That is, if, in addition to the septic vibrio, there are present common aërobic bacteria, the latter by developing, prepare the way for the former. Thus it is that the vibrio develops in the intestinal canal, which is ordinarily destitute of oxygen, and Pasteur here recognized once more the rôle played by associations of bac-

<sup>1</sup> Rice and some other seeds are now known to germinate in this way. See paper by Takahashi. Bull. Imp. Agr. Col., Tokyo, 1905. Vol. 6, p. 439, *Trs.*

teria which we have dwelt upon throughout this book and which he understood so well.

Preoccupied as he was with the application of these facts to medicine, he could not fail to write, at this stage, the following lines, the advantage of which we shall find once more at the end of this chapter.

“A curious therapeutic observation presents itself. Let us suppose a wound exposed to the air and under putrefying conditions leading to the accident of simple septicemia in the patient, I mean without other complications than would result from the development of the septic vibrio. Theoretically, at least, the best means of preventing death would be to wash the wound unceasingly with common aërated water, or to flood the surface with atmospheric air. The adult septic vibrios, about to divide by fission, would die in contact with the air; as to their germs, they would not grow. Furthermore, one might expose the surface of the wound to air heavily charged with the germs of the septic vibrio, or wash it with water holding in suspension billions of these germs without producing the least septicemia in the patient. But under similar conditions let a single clot of blood, or a single fragment of dead flesh, lodge in a corner of the wound sheltered from the oxygen of the air, where it remains surrounded by carbonic acid gas, even though it might be over a very small area, and beginning at once the septic germs will give rise, in less than 24 hours, to an infinite number of vibrios multiplying by fission and capable of causing in a very short time a mortal septicemia.”

And immediately, through the door he has opened, he passes a whole series of similar cases. There is, for example, in common waters from the most varied sources, another vibrio both aërobic like the bacteridium of anthrax and anaërobic like the septic vibrio,

inoculation of which into a guinea pig produces pus collections or abscesses, that is to say, a pathological condition very different from that produced by either the anthrax bacillus or the septic vibrio. Its power of producing pus is so great that it still does so even though the inoculation is made after the vibrio has been killed by the action of heat and thus it behaves like an inert body. This should interest you, you medical men, we seem to hear Pasteur saying, for, with this organism one can obtain those celebrated metastatic abscesses which have puzzled you so much from the time of Hippocrates. When it is inoculated, living or dead, into the veins so that the circulation will distribute it throughout the tissues, we see the lungs, the liver and other organs filled within 24 hours with an infinite number of metastatic abscesses in all stages of development. Why should it be astonishing that a diseased organ can do the same thing in a living being, if it empties its parasites into a blood vessel?

Here again, as is always the case in ordinary water and in the air, there are other anaërobic vibrios which, when introduced into the tissues, do not develop there for various reasons: in one case, because the normal temperature of the body is too high; in another case, because the healthy tissues are too well supplied with oxygen. But diminish in any way whatsoever this *vital resistance*, which, mark my words, has no abstract significance in my discourse, and always represents a concrete force, and you will see these microbes hitherto dormant, take possession of the organism and combine their actions and efforts to produce purulent septi-cemias or purulent septic infections. These are the enemies with which we are threatened on all sides in ordinary life, and to which we are still further exposed when the surgeon intervenes and causes or repairs lesions

in the tissues. "This water, this sponge, this lint with which you wash or cover a wound, deposit germs there which, as you see, have an extreme facility for multiplying within the tissues and which would infallibly cause the death of the patient in a very short time, if the body by its vital processes did not check the multiplication of these germs. But alas, how many times this vital resistance is impotent, how often the constitution of the wounded man, his weakness, his morale, and bad dressing of the wound oppose only an insufficient barrier to the invasion of these infinitely small organisms with which, unwittingly, you have entirely covered him in the injured part. If I had the honor to be a surgeon, impressed as I am with the dangers to which the patient is exposed by the germs of microbes scattered over the surface of all objects, particularly in hospitals, not only would I use none but perfectly clean instruments, but after having cleansed my hands with the greatest care and subjected them to a rapid flaming, which would expose them to no more inconvenience than that felt by a smoker who passes a glowing coal from one hand to the other, I would use only lint, bandages and sponges previously exposed to air of a temperature of  $130^{\circ}$  to  $150^{\circ}$  C.; I would never use any water which had not been subjected to a temperature of  $110^{\circ}$  to  $120^{\circ}$  C. All this is very practical. In this way, I would only have to fear the germs in suspension in the air around the bed of the patient; but observation shows us daily that the number of these germs is, so to speak, insignificant in comparison with those distributed in the dust on the surface of objects, or in the clearest ordinary water. And, furthermore, nothing should prevent the use of antiseptic methods in dressing wounds, but, joined with the precautions I have indicated, these methods of procedure could be very greatly simplified. A weak phenic acid,

which consequently does not affect the hands of the operator, or cause him trouble in breathing, could be advantageously substituted for a caustic phenic acid."

It was in this way, scarcely raising the tone of his voice, and without any high sounding phrases but merely by following rigorously and patiently the thread of his thought that Pasteur compelled surgeons to perfect the methods for dressing wounds which had been employed by Lister, and which had themselves been such a great discovery. These methods had been inspired by an inexact idea as to the true state of affairs, an idea which Pasteur had shared, as we have seen, but from which he detached himself, more and more. This idea was that the air, especially, was to be feared as the conveyor of germs. In this memorable note, we have Pasteur laying the blame upon the sponges, the lint, and, without wishing to put it into so many words, upon the surgeon himself.

To make this idea acceptable to the illustrious practitioners, his colleagues in the Academy of Medicine, that they were responsible for the accidents which occurred to their patients, and that when there was a case of death by purulent infection in their service, or even merely a case of operative fever it was their fault, was a task that Pasteur had not ventured to assume, and yet one which he accomplished; because *the new was certain to destroy the old*, because it was only necessary to leave to itself the idea lodged in this Note in order to see it invade and overthrow everything. Modern surgery has arisen full fledged from this Note of 1878, the general outlines of which we have just traced.

"Some weeks ago," said Pasteur in conclusion, "one of the members of the Section of Medicine and Surgery of the Academy of Sciences, M. Sédillot, after long meditation on the things he had learned in the course

of a brilliant career, did not hesitate to declare that success and failure in surgery found a rational explanation in the principles on which rests the so-called theory of germs, and that this would give rise to a new surgery, that already inaugurated by a celebrated English surgeon, Dr. Lister, who was one of the first to understand its fecundity. Without any professional competence, but with the conviction of a qualified experimenter, I venture to repeat here the words of our eminent confrère."

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## XI

### NEW EXAMPLES OF PHYSIOLOGICAL CONFLICTS

In this rapid review of the etiological work of Pasteur I have naturally omitted some details which seem to me secondary, and some ideas which would have constituted merely replicas of ideas already well-known. Pasteur studied, or caused to be studied under his eyes, all the bacteria which he could find, however little pathogenic they were or appeared to be. As I have said, that which interested him was the pathological conflict between the physiological properties of the micro-organism and of the cells of the tissues, and for examples of this conflict he searched everywhere.

As the laboratory was not a hospital we scarcely saw diseases there; he was obliged to profit by the indispositions of the personnel. I was, just at this moment, beset by a series of boils and the first thing that Pasteur did when I showed him one of them was to prick it, or rather have it pricked, for he was not fond of operating himself, and to take therefrom a drop of blood in order to make a culture, in which undertaking he was successful. A second boil gave the same result, and thus the staphylococcus was discovered which since that time

has been so well known. He found the same microbe, made up of little agglomerated granules, in the pus of an infectious osteomyelitis which M. Lannelongue had submitted to him for examination, and we see him, declaring immediately with a fine audacity that the osteomyelitis and the boil are two forms of one and the same disease, and that the osteomyelitis, which is a suppuration of the marrow, is the boil of the bone. What could be worse than to liken a grave malady taking place in the depths of the tissues to a superficial malady, which is generally trifling! To confound internal and external pathology! When he launched this opinion before the Academy of Medicine, I picture to myself the physicians and surgeons present at the meeting staring at him over their spectacles with surprise and uneasiness. Nevertheless, he was right, and this assertion, daring at the time, was a first victory of the laboratory over the clinic.

A second followed straightway: "In the puerperal infections, the pus of the uterus, that of the peritoneum, and the blood-clots in the veins contain a microbe occurring in the form of rounded granules arranged in chains. This chaplet-like aspect is especially apparent in the cultures. Pasteur does not hesitate to declare that this microscopic organism is the most frequent cause of infections among women in confinement. One day, in a discussion on puerperal fever at the Academy of Medicine, one of the most renowned of his colleagues made an eloquent dissertation on the causes of epidemics in the maternity hospitals. Pasteur from his place in the audience interrupted him: 'The cause of the epidemic is nothing of the kind! It is the doctor and his staff who carry the microbe from a sick woman to a healthy woman!' And when the orator replied that he was convinced that no one would ever find this



microbe, Pasteur darted to the blackboard and drew the organism with its chaplets, saying: 'There! There is its picture!' His conviction was so strong that he could not refrain from expressing it forcibly. One can scarcely understand to-day the surprise, and the stupefaction, even, of the medical men and their students when at the hospital, with a simplicity and an assurance which seemed presumptuous in a man who was entering a lying-in hospital for the first time, Pasteur criticised the methods of dressing wounds, and declared that all bandages should be placed in a sterilizing oven. Furthermore, he maintained that he could tell by examination of the lochia, which women would have an attack of puerperal fever, and he assured them that in a woman who was very badly infected he could demonstrate the microbe in the blood of the finger. And he was as good as his word. In spite of the tyranny exercised by the medical education which weighed heavily at that time on the minds of the students, some of them were captivated and came to the laboratory to observe at closer range those methods which afforded diagnoses so exact and prognoses so sure."<sup>1</sup>

I will cite only one more fact, which in some degree forms a connection with what is to follow. In the course of this search for microbes which has been so fruitful, Pasteur encounters a bacterium which cannot develop under the skin because the temperature of the human body is a little too high for it. Immediately his thought reverts to the anthrax bacteridium which is unable to develop in birds, and he asks himself if this does not result from the high temperature of these animals, which is always in the neighborhood of 42° C. What would happen if one could lower the temperature of

<sup>1</sup> L'Œuvre médicale de Pasteur, par le Dr. E. Roux, Agenda du chimiste, 1896.

an inoculated chicken some degrees? The success of the experiment was immediate. A chicken, the feet and hind quarters of which were plunged into water at 25° C., so that the temperature of its whole body was lowered to 37–38° C., which is the temperature of animals susceptible to anthrax, died of this disease, although resistant to it under normal conditions. If the chicken is taken from the water and heated at the time when the first symptoms of invasion of the tissues appear, it triumphs over all the parasites and recovers. Later Gibier made the reverse experiment, giving anthrax to frogs which are not susceptible to this disease because they are cold-blooded animals, the body temperature being too low. To accustom them little by little to living in warm water, suffices to render them capable of succumbing to anthrax when their body temperature has been thus raised. The interpretation of these two facts is less simple than Pasteur supposed it to be and we shall meet them again very soon in connection with variations in virulence. I cite them only as further evidence of his tendency to relegate everything as much as possible to the domain of physics and chemistry, to study, in the light of these two sciences, the physiological properties of the microbe and to oppose these properties to those of the tissues.

However broad-minded one may be, he is always to some extent the slave of his education and of his past. It is clear that Pasteur inclined naturally to the side of chemistry, and there were not lacking men to reproach him for this. To this chiding he always disdained to respond. Doubtless he thought it was not worth while, and that he must be content to pity those who believed it possible for a vital problem to be something other than a problem of physics and chemistry. This will be still more evident in the study which we shall make of virulence.





PASTEUR

(Int. Med. Congress at Copenhagen, 1884.)

(Courtesy of Capt. J. C. Pryor, Naval Med. School, Washington,  
D. C.)

## EIGHTH PART

### THE STUDY OF VIRUSES AND VACCINES

#### I

#### MICROBIAL DISEASES AND VIRUS DISEASES

What idea could one have, about 1880, of virulence as we understand it to-day? The answer is easy if one is willing to regard it from the point of view of our actual knowledge. Considerable variation in virulence had been determined in various microbial diseases, but it was not known whether they had the character of the virus diseases, that is, would not recur in the same individual. For the true virus diseases, such as small-pox and cowpox, the established variations in virulence were feeble, and supposed to be dependent, as we have seen, on external conditions, which amounts to saying that they were unexplained.

This point of view shows us clearly the difficulties of the question, but it is not from this standpoint that our observations should be made. What could one think at that time concerning the relation between microbial diseases and the virus diseases, is what we must ask ourselves. Strange to say, one thought nothing! These were two territories separated by an arm of the sea over which there was no bridge. From one of the continents a person might indeed from time to time glimpse the other and observe its outlines, but both seemed isolated and equally impenetrable.

For Pasteur alone, the man of the large horizons, they were in some places in contact. The careful

reading of the works of Jenner and his followers had left a profound impression on the mind of the master, and by correlating incessantly in his thoughts the teachings of the books and those of the laboratory, he had formed a general impression which I desire to summarize, relying not simply on my own recollections, but also on that of his collaborators at this memorable time.

On the subject of variation in power of microbes to attack there existed only the curious results obtained by Coze and Feltz in 1869, confirmed since then by Davaine for the anthrax bacteridium, and especially for the disease of Leplat and Jaillard. The virus increased in strength by passage through the organism. The blood of the first animal inoculated was fatal to a second only in a dose, let us say, of one-tenth of a drop. The fatal dose decreased little by little with successive animal passages to that of a hundredth, a thousandth, a millionth of a drop. This fact was the only one of its kind. It was eminently curious and suggestive. It would have been more so if there had not been needed, in order to realize it, the coöperation of the organism, at cross purposes with which everything becomes obscure. Men so little dreamed of ascribing the increased virulence to its true origin, the microbe itself, that when Pasteur, in his study of the septic vibrio, finds cultures which prove to be unequally active in animals, his first thought is that he has two or several septic vibrios of unequal virulence, which the cultures have separated more or less completely. Under this impression he carried on investigations for a long time without result. It was only when he discovered that a simple change in culture method, namely, the substitution of a blood serum slightly charged with coagulated fibrine for Liebig's bouillon, suddenly increased the virulence of a vibrio

which for 20 or 30 generations had shown itself to be attenuated, that he accepted the idea that these variations depended on one single vibrio and its culture medium.

It was a great step indeed; but beyond this there was nothing, and in order to see farther it was necessary to consider the virus diseases. The latter presented facts analogous to those of Coze and Feltz, and Davaine. It was known that there were benign epidemics of smallpox and others that were deadly, that the severity was variable in the course of the same epidemic, and generally diminished as it drew to a close. It was also known from the practise of smallpox inoculation, resorted to before the time of Jenner, that inoculation from a benign case of smallpox ordinarily produced a smallpox still more benign, but this was not always true, for sometimes the inoculated patient died.

The vaccine introduced by Jenner had been a wonderful discovery, but it had made the veil still thicker behind which the virus diseases lay concealed. With it variations in virulence were scarcely to be feared. After being very clearly diminished in passing from the cow to the man, the virulence of the vaccine was maintained very constantly from arm to arm, for a long series of generations. But if there was something immutable in the severity of the disease or in its period of evolution, there was, on the contrary, great variation in the duration of the immunity which it produced. So that, to sum up, the ideas which seem to us to-day the most closely related, the most coherent, were at that time scattered and contradictory, and no one attempted to correlate them.

It is here that Pasteur experienced the benefit of his former studies and of facts which he alone knew, since he had published them only in part, and in that

somewhat dogmatic style, general and without details, which he still affected at this time. I speak of his study of *chicken cholera*, concerning which I have as yet said only a word, and which I have reserved for the following chapter, because it is a disease which has the closest analogies with the virus diseases. We shall see, in reality, that this cholera, like smallpox, is sometimes epidemic and deadly; sometimes chronic and harmless; that transferred from the chicken to the guinea-pig, like the cowpox transferred from the cow to the man, it may become an artificial and fixed disease, preserving its character indefinitely.

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## II

### CHICKEN CHOLERA

“Sometimes there breaks out in the poultry-yard a disastrous disease, commonly known as chicken cholera. The animal which is a prey to this infection is without strength, trembles and has drooping wings. The feathers of the body are ruffled giving it the form of a ball; an unconquerable drowsiness overpowers it; if forced to open its eyes it appears to waken from profound slumber; soon the eyes close again, and in most cases, the animal does not change its position until death comes, after a dumb agony. At most it sometimes shakes its wings for a few seconds.”<sup>1</sup>

These singular symptoms are due to the development of a microbe which can be isolated in cultures in neutralized chicken bouillon. Sowing in this liquid a drop of the blood of a chicken which had died of the cholera,

<sup>1</sup> Sur le choléra des poules. Comptes rendus de l'Académie des Sciences, 1880.



and working as he had done with anthrax blood, Pasteur saw develop everywhere small non-motile segments of an extreme tenuity, slightly constricted in the middle (Fig. 22), and clearly approaching, much more than the anthrax bacteridium and the other bacilli, those microscopic granules to which Chauveau had attributed the active rôle in the virulent humors of cowpox, smallpox, and sheeppox.

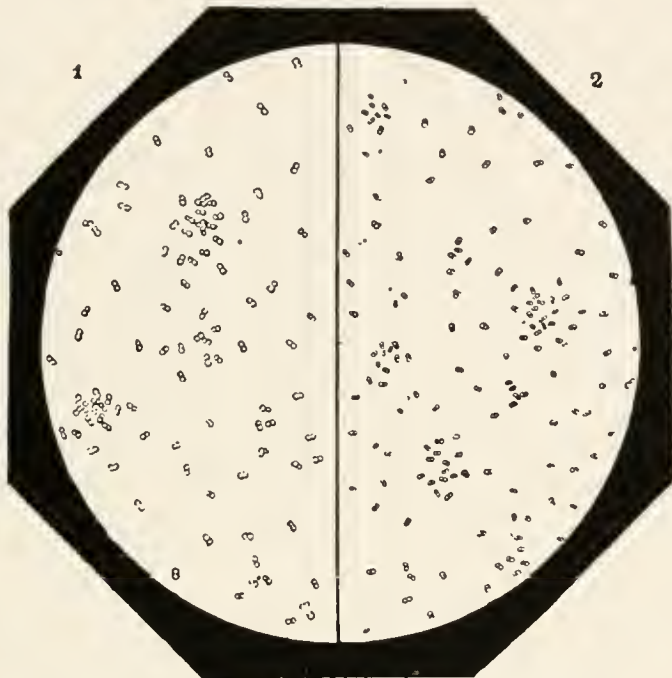


FIG. 22.—Microbe of chicken cholera.  
Young. Old.

This organism is so tenuous that the precipitate which it forms at the bottom of the flask is sometimes almost invisible; it appears scarcely to touch the nutritive substances placed at its disposal, and one might ask himself the question whether it changes in any respect the culture fluid. "Let us try," said Pasteur to himself; and he tried, and saw with surprise that if this bouillon culture was filtered by passing through a porous wall in order to remove from it all the parasites, and then re-inoculated, no growth took place. The

first culture has rendered the medium unsuitable for a second, as the first attack of a virus disease protects against all new attacks. Thus was sown in the mind of Pasteur, a seed which fell on good ground and could not fail to be productive.

Inoculation with this organism is usually fatal but it sometimes happens that the chicken, after having been sick, seems to recover. Nevertheless it eats little, its comb loses color, it grows thin, and finally it succumbs after weeks or months of languor. Is it always the same disease? Yes, for the organism which we find in the tissues, if isolated, kills the chickens into which it is inoculated. Why, then, did it not cause the death of the chicken which carried it? Whence comes this relative immunity? Pasteur was not yet able to answer this question, but he already had the right to put it to himself. While waiting to find the solution, he pointed out the analogy between these larval forms of the cholera, and the grave and often incurable forms of certain virus diseases, such as measles, scarlatina, and typhoid fever.

Many ideas are already knocking at the portals of his mind: and this is not the end. The chicken is not the only domestic animal capable of offering a habitat to the microbe. The dog, the horse, and many animals of the barnyard are also inoculable. The rabbit is particularly susceptible, and Pasteur discovered later that the contagion could be propagated in terriers. The guinea-pig, on the contrary, is quite resistant. It succumbs to inoculations in the veins, but those under the skin produce scarcely more than a slight abscess, which bursts spontaneously and heals without making the animal which bears it appear sick. This abscess is a kind of pure culture of the microbe, and if we inoculate a little of its contents into chickens, "these chickens

die quickly, while the guinea-pig which furnished the virus, recovers without the least suffering. We are present here, then, at a restricted evolution of a microscopic organism which causes the formation of pus and a closed abscess without bringing about any internal disturbance or the death of the animal on which it occurs, and, nevertheless, one which is always ready to convey death to other species into which it is inoculated, ready even to kill the animal on which it occurs in the form of an abscess, if more or less fortuitous circumstances enable it to pass into the blood or into the splanchnic organs.

“Chickens or rabbits which live in the company of guinea-pigs bearing such abscesses may suddenly become sick and die without the health of the guinea-pigs appearing to be in the least impaired. For this to occur, it is only necessary that the abscesses of the guinea-pigs should rupture, scattering a little of their contents on the food of the chickens and the rabbits. An observing person, seeing these facts and ignorant of the relation of which I am speaking, would be astonished to see chickens and rabbits destroyed without any apparent cause, and would believe that the disease was spontaneous, for he would be far from supposing that it had originated in the guinea-pigs, all in good health, especially if he knew that the latter are also subject to the same disease. How many mysteries in the history of contagions will some day receive solutions still more simple than that of which I have just been speaking! Let us reject theories which we can contradict by convincing facts, but not on the vain pretext that certain of their applications escape us. The combinations of nature are at the same time more simple and more varied than those of our imagination!”

For anyone who pondered over Jenner's work, what was

more analogous than these facts with what was known on the subject of those apparently spontaneous sudden appearances on the horse, on the cow, on the hands of the milkers, that is, those eruptions of *horsepox*, of *cowpox*, and of *vaccinia*? What more natural than to see in smallpox and vaccinia different manifestations of the presence of the same microbe, or at least of two closely related microbes? In all these cases, the ideas regarding microbial diseases and those concerning virus diseases are more and more bound together. Pasteur has just spoken of the imagination. He had much of it, and he allowed it to have full play on this subject. He did not even scorn the dream. "I take the liberty" he said one day, "of recalling to my confrère, M. Blanchard, that the illusions of an experimenter form a great part of his power. These are the preconceived ideas which serve to guide him. Many of them vanish in the long path which he must travel, but one fine day he discovers and proves that some of them are adequate to the truth. Then he finds himself master of facts and of new principles, the applications of which, sooner or later, bestow their benefits."<sup>1</sup>

The hour had come for him to enter the enchanted grotto full of treasures.

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### III

#### DISCOVERY OF VACCINES

The first experiments on chicken cholera date from 1879. Interrupted by vacations, they had been resumed, but were upset at once by an unforeseen obstacle. Almost all the cultures left in the laboratory had become sterile.

<sup>1</sup> Comptes rendus de l'Académie des Sciences, 1<sup>er</sup> sem., 1880.

As all these belonged to the experiments under way, an attempt was made to revive them, and with that end in view, transfers were made from them either into chicken bouillon or into chickens. Many of these made no growth, and also spared and left unimpaired the animals into which they were inoculated, and we were about to throw them away, in order to begin anew, when it occurred to Pasteur to inoculate a fresh young culture into these chickens which, at least in appearance, had so well resisted the inoculations with the cultures made the preceding summer.

To the surprise of all, perhaps even of Pasteur himself, who did not expect such a success, almost all of these chickens resisted, whereas new chickens, just brought from the market, succumbed in the ordinary length of time, thus showing that the culture used for the inoculation was very active. With one blow, chicken cholera passed to the list of virus diseases and vaccination was discovered! What secret instinct, what spirit of divination impelled Pasteur to knock at this door, which was only waiting to be opened? Here we see clearly the part played by his readings and his former studies, by the incessant ponderings which had been going on in his mind, and by the intervention, in the midst of these obscurities, of this faculty of imagination to which he has referred in the lines that precede, lines written just at the time when he was setting forth, a conqueror, in the realm of his dream.

He had, in reality, just established between certain microbial diseases and the virus diseases a definite connection which it was to be the task of the future to enlarge and consolidate. There were, then, microbial diseases which did not recur! One could, therefore, prepare vaccines insuring protection against a virulent inoculation! Prudently, Pasteur refrained from

saying how he obtained this vaccine. He preferred to insert in the Note in which he announced the preceding fact, another fact not less astonishing, to wit, that this vaccine, once developed, could be reproduced indefinitely by cultures, with all its vaccinal properties, or with what has since been called its degree of attenuation.

If one can say, strictly speaking, that Pasteur had had a presentiment of the first of these facts, the latter at least was entirely unforeseen. It is, or seems to us at least, entirely independent of the other, and it is possible that vaccination would still be in force even if the latter did not exist. But it was none the less valuable in practice, and Pasteur in running across it must have recalled the history of Jenner, and even have re-lived it. And here is my reason!

It is well known that Jenner, after having discovered that inoculation with *cowpox* gave protection against smallpox and became a vaccine, had had some anxiety regarding it. He feared, in the first place, being obliged to return to the cow and to the cowpox to obtain his vaccine, and this prospect was scarcely calculated to please him. According to his idea, cowpox was inoculated into the cow by a milker affected with smallpox, was found only in the female and at the points touched by the milker, that is on the udder, and represented consequently the bovine form of human smallpox. If this were so, there must be smallpox in order to produce cowpox, and as, theoretically, the vaccine suppressed the smallpox, here was a vicious circle. Jenner sought, therefore, with an emotion of which we find traces in his memoirs, to obtain from man the material for inoculation, the vaccine, *to vaccinate from arm to arm*, and he succeeded. It was his chief discovery, and one which makes for his eternal glory. But the same history repeated itself in Pasteur nearly a century later and

there was this further resemblance that the absolute conservation of the virulence was realized neither by the vaccine transferred from arm to arm, as Jenner believed, nor by the chicken cholera vaccine, transferred from culture to culture, as Pasteur believed. In both cases, there is a deterioration, but a very slow one, which it has required years to perceive.

In any event, a new world was opened to him, and he must push on into it eagerly. This is what Pasteur did with the incomparable authority of a master, constantly guided, it is true, by the then prevailing notions regarding virus diseases, but having as a means of illuminating his every step those methods for cultivating the virus which were entirely his own. I have no intention of following up his study of chicken cholera; I should like, merely, to point out the principal facts, those which should not be forgotten because they tell us, in a particularly simple case and one which has been well worked out, what a virus disease really is.

If we inject a few drops of a young culture of the microbe of chicken cholera into one of the large pectoral muscles of a chicken, or inject them into its blood, or still better, put them on the food, on the bread or the meat, we shall see, after a time varying with the path of entrance, the symptoms of the disease appear in this fowl. The animal loses its appetite, becomes drowsy, ruffles itself into a ball and dies sometimes in 24 hours, entirely invaded by the microbe, which is found in its blood and in all its organs.

Instead of using a young culture for inoculation, let us repeat the experiment with a culture several weeks old. We shall still have a disease marked by loss of appetite, drowsiness, and ruffled feathers, but the chicken does not die. After some days of more or less severe illness, it apparently fully recovers. There has been,

however, a development of the microbe, since there has been disease, and, in reality, when this disease is in progress, the organism can be found at the point of inoculation and in all the tissues, but this time it has not caused death. The chicken has repelled the attack.

Has, then, this benign cholera played in the chicken the rôle of the benign smallpox or vaccine in man? Yes, for this chicken is henceforth immune to inoculation with the youngest and most virulent culture of the micrococcus. It has been vaccinated against the cholera.

Let us continue this study which has already proved so fruitful. Since the power of action on the organism diminishes with the age of the culture, let us make our inoculation from a very old culture, one which is near the point of death. The microbe, still alive, can still cloud the bouillon into which it is sown. It does this slowly, but life and virulence are not synonymous in this case, for the organism is absolutely incapable of developing in the body of a chicken, or communicating to it even the slightest disease. Here it is the chicken which overcomes and kills the inoculated microbe straightway. The latter, in spite of its specific origin, entirely resembles, therefore, those thousands of species of micrococcus which are met with everywhere on the surface of the body, which fill the intestinal canal, and which are always harmless. It is, nevertheless, that same microbe which some weeks before killed ten chickens out of ten. A virus, then, is not that entity, not that unity, which it was considered to be by the old physicians. It is in a state of perpetual evolution, of continuous variation, due to wholly natural causes.

Let us take, now, this last chicken which suffered no inconvenience from the inoculation with our dying virus, and let us try to inoculate it with the virulent virus; it behaves toward this exactly as a new chicken



would; it dies, or at least is very sick, the extent of the disease and the danger of death being in inverse ratio to the amount it had suffered in the previous inoculation, for the slightest disease produced by inoculation serves as some protection.

Instead of making the three experiments which precede, we might, clearly, arrange a greater number extending over the period of life of the virus, six, ten, etc., in other words, interpose between the most sensitive animal and the most resistant, a whole series of animals differing in degree of immunity, each one of which will acquire a degree of immunity corresponding to the amount of vaccine which it can endure without dying. The more severe the disease the greater the protection the disease will afford it.

All these animals, identical in appearance, different in reality, clearly behave in a very different manner toward the same microbe of virulent cholera. Some, vaccinated, resist it without any trouble. Others, little vaccinated or only recently, will become sick or die. Furthermore, an animal, vaccinated or not, behaves very differently toward microbes of unequal attenuation. It is the variable result in this conflict which makes the variety of pathological cases, and there are not on the palette of any painter colors enough to designate the innumerable differences in receptivity which we find in the virulent diseases.

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#### IV

#### ANTHRAX IS ALSO A VIRUS DISEASE

As the study of chicken cholera progressed Pasteur devoted much thought to anthrax on which he was working at the same time. He wished to study its etiology, to

determine precisely the means by which the bacteridium passes from one animal to another, to discover how the disease can be at the same time endemic and epidemic, can have more or less periodic awakenings, or lie dormant for long years. Koch had already outlined this subject, and Pasteur had to content himself with adding the finishing touches, but these touches are the work of a master. We shall be thoroughly convinced of that when we note the principal facts.

Koch had shown how the spores are formed when an animal, dead of anthrax, is buried, but he had never found them in the earth, nor did he know how long they lived there. Pasteur succeeded at the outset in isolating the bacteridium of anthrax from the myriads of germs which accompany it in the soil, always employing for this purpose the same method: that of pure cultures in the medium best fitted to the physiological needs of the anthrax bacillus. These experiments date from 1881. The method of making cultures on solid media, conceived by Koch, was not yet known in the laboratory, having been published only that year. It would certainly have simplified the problem and facilitated the researches, but we see, as has since been admitted, that it was not indispensable for studies of this kind, and that Pasteur extricated himself from his difficulties without it. It is true that another would probably have failed.

Thanks to this method, Pasteur discovers that the anthrax spores can persist a long time in the vicinity of the place of burial, and that they can be found there after a period of 12 years, as virulent as on the first day. This gave birth to a new problem. How can these spores on the soil of the burial pit resist the rain which engulfs them, the wind which sweeps them away, and, we should add, to-day, the light of the sun, which is more

active on them than its heat. This might be conceived as due to intermittent cultures which renew and multiply the spores, but there is no probability in such an explanation, the soil, rich in vegetable matter, being full of organisms which are much better prepared than the anthrax bacteridium to profit by the slightest condition favorable to bacterial growth. Pasteur was seeking an explanation in some other direction, but he knew not where. The solution came to him by intuition one day, in the course of a walk. "It was after the harvest; there remained only the stubble. The attention of Pasteur was drawn to a portion of the field because of the difference in the color of the soil. The owner explained that some sheep which had died of anthrax had been buried there the preceding year. Pasteur, who always investigated things very closely, observed on the surface of the soil a multitude of the tiny castings of earthworms. The idea occurred to him then that in their continual journeys from the depths to the surface, the worms brought with them soil rich in the humus which surrounds the carcass of the animal, and with it the anthrax spores which it contains. . . . Pasteur never stopped with theories; he immediately proceeded to experimental work. The latter justified his suppositions, the earth from one of the worms when inoculated into guinea-pigs gave them anthrax."<sup>1</sup>

These spores, brought to the surface of the soil in this way, contaminate vegetation and reach by way of food and drink the digestive canal of the farm animals. Sheep which are kept over the spot where a victim of anthrax is buried, easily contract anthrax, especially if their food contains chaff, stubble, awns, or small prickly

<sup>1</sup> L'Œuvre médicale de Pasteur, par le Dr. E. Roux, *Agenda du chimiste*, 1896.

or sharp substances, capable of injuring in places the epidermis of the intestinal canal, and of thus breaking the natural barrier opposed to the invasion of the germs. The symptoms of the disease thus provoked are those of the disease as it occurs naturally, so that, as Koch had conjectured, it is especially through the food that contagion takes place. And it is thus that the disease may be at the same time endemic and epidemic, and may render certain regions and certain fields dangerous, without causing any trouble in their vicinity.

All these researches, as the reader divines, had been carried on for the sake of establishing a prophylaxis for anthrax, and already a certain number of practical conclusions could be drawn regarding precautions to be taken in burying an animal affected with anthrax. These were abruptly broken off as soon as there appeared the first intimations of the possibility of a vaccination for anthrax. Was, then, anthrax also a virus disease, not prone to recur?

This question was solved for Pasteur as soon as it was stated. Furthermore, his solution was published without anyone's having observed it in the Note in which it was inserted. In this Note of July 12, 1880,<sup>1</sup> devoted to the etiology of anthrax, Pasteur had in reality introduced, almost in parenthesis, and without explaining at all its place in this question, a phrase in which he had incidentally pointed out this fact: When 8 sheep, which had been subjected to a prolonged sojourn on a spot where an anthrax victim had been buried and had proved resistant, were inoculated at the close of the experiment with a culture of virulent anthrax, several of them survived, whereas fresh sheep of the same race succumbed almost without exception to the same in-

<sup>1</sup> Sur l'étiologie du charbon (en collaboration avec MM. Chamberland et Roux). Comptes rendus de l'Ac. des Sciences, t. XCI, 1880, p. 86.

oculation. This fact had remained in the mind of Pasteur as a question, and he had believed that he could solve it. Afterwards, calling to mind that chickens, fed upon food contaminated by the cholera organism, do not always die and are sometimes found to be vaccinated when they survive, he had asked himself if the sheep in the preceding experiment had not acquired their immunity through a former contagion caused by food. But then, according to this hypothesis, anthrax was a disease which would not recur.

Later something else occurred to confirm him in this idea. In a series of experiments made with Chamberland in the Jura,<sup>1</sup> in order to test the value of a cure for anthrax, he had had the opportunity of seeing two cows become very sick as the result of a trial inoculation, but, having resisted, endure without any apparent difficulty a virulent inoculation which made very ill or even killed fresh animals not previously prepared.

All this proved to Pasteur that anthrax was a virus disease, and now the only question was how to find its vaccine. Naturally, he turned first to the method which had been successful with chicken cholera, and tried to let the bacillus become old in its culture medium. But immediately a difficulty arose, that is, the anthrax bacillus very quickly transformed itself into spores, and the spore does not grow old; the spore is a "seed," and for a seed, time is almost suspended.<sup>2</sup> It was,

<sup>1</sup>Sur la non récidence de l'affection charbonneuse (en collaboration avec M. Chamberland). Co. rend. de l'Ac. des Sci., t. XCI, 1880, p. 533.

<sup>2</sup>It is not known how long seeds or spores will live under favorable conditions. Dr. W. J. Beal buried 25 varieties of weed-seeds in sandy soil in bottles of earth, mouth down, and found some individuals of 11 varieties alive after 25 years, but they germinated very irregularly. The senior writer put spores of the hay-bacillus into concentrated glycerin, exposed to the air in a cotton-plugged test tube, 10 years ago and a very few are still living. *Trs.*

therefore, necessary to prevent spores from forming, at the same time keeping the bacillus alive. This can be accomplished in different ways, the first successful method being the use of antiseptics. That did not satisfy Pasteur. He wished a second edition of the chicken cholera. He searched in another direction and finally discovered that it sufficed to keep the culture in a shallow layer of neutral chicken bouillon at 42-43° C.

We then see reproduced the same phenomena as in chicken cholera. After a month passed under these conditions, a little extreme as to temperature, the bacteridium is dead, that is to say, the best culture medium inoculated with it remains sterile. After 8 days, cultures are still made from it readily and give abundant growth, but the organism is harmless to the guinea-pig, the rabbit, and the sheep, three species most susceptible to anthrax. Before the virulence is lost, it passes in the course of about a week through all degrees of attenuation, and, as in the case of the chicken cholera organism, each of these grades of attenuated virulence may be indefinitely preserved through cultures. Thus vaccines were created. Nothing is easier than to find in these graded viruses the means of giving to sheep, cows, and horses a benign fever, capable of preserving them afterwards from the fatal disease.

These vaccines had in this respect a practical importance very much greater than those of chicken cholera. The victims of anthrax were counted by thousands in France alone, and the losses were reckoned in millions. Anthrax vaccination could remedy all this but before bringing about its acceptance, what trouble, what time, what efforts to convince the public, the veterinarians and the farmers! Here it is that we shall find again Pasteur the apostle, whom we have seen in action after his studies on the silkworm, the Pasteur who

would have wished to be everywhere, to see everything, and to rely on no one. He had opened the campaign in an almost startling manner with that famous experiment at Pouilly-le-Fort, which so impressed everybody. I shall borrow the account from M. Roux, who saw it and collaborated in it.

“The Society of Agriculture of Melun had proposed to Pasteur a public trial of the new method. The program was arranged for the 28th of April, 1881. Chamberland and I were away on a vacation. Pasteur wrote to us to return immediately, and when we were reunited in the laboratory he told us what had been agreed upon. Twenty-five sheep were to be vaccinated, and then inoculated with anthrax; at the same time 25 other sheep would be inoculated as checks; the first would resist; the second would die of anthrax. The terms were exact; no allowance was made for contingencies. When we remarked that the program was severe, but that there was nothing to do except carry it out since he had agreed to it, Pasteur replied: ‘What succeeded with 14 sheep in the laboratory will succeed with 50 in Melun.’

“The animals were collected at Pouilly-le-Fort, near Melun, on the property of M. Rossignol, a veterinarian who originated the idea of the experiment and who was to watch it. ‘Be sure not to make a mistake in the bottles,’ said Pasteur gaily, when on the fifth of May, we were leaving the laboratory in order to make the first inoculations with the vaccine.

“A second vaccination was made on the 17th of May, and every day Chamberland and I would go to visit the animals. On these repeated journeys from Melun to Pouilly-le-Fort, many comments were overheard, which showed that belief in our success was not universal. Farmers, veterinarians, doctors, followed the experi-

ment with active interest, some even with passion. In 1881 the science of microbes had scarcely any partisans; many thought that the new doctrines were baleful, and regarded it as an unexpected piece of good fortune that had drawn Pasteur and his staff out of the laboratory to be confounded in the broad daylight of a public experiment. They were going then with one blow to put an end to these innovations, so compromising to medicine, and to find again security in the same traditions and ancient practices, for a moment threatened!

“In spite of all the excitement aroused by it, the experiment followed its course; the trial inoculations were made the 31st of May, and the rendezvous was appointed for the second of June to determine the result. Twenty-four hours before the time decided upon, Pasteur, who had rushed into the public experiment with such perfect confidence, began to regret his audacity. For some moments his faith was shaken, as though he feared the experimental method might betray him. A mental tension too long continued had brought about this reaction, which, however, did not last long. The next day, more assured than ever, Pasteur went to verify the brilliant success which he had predicted. In the multitude which thronged that day at Pouilly-le-Fort, there were no longer any who were incredulous; only admirers.”

This fine success<sup>1</sup> did not immediately bring conviction. He had to repeat the experiment in different places in France and abroad, in order to convince those who wished to touch and to see before believing. Nothing can give an idea of the activity of Pasteur at this time. To the life within the laboratory, which continued

<sup>1</sup> Fourteen days after the second vaccination the 50 animals were inoculated, all in the same way from the same virulent culture, and 2 days later, as Pasteur had predicted, the 25 vaccinated animals were unharmed and the 25 unvaccinated animals were dead. *Trs.*



at full flood, and where studies on rabies had already commenced, was now added a public life not less active. He must superintend the manufacture and the sending out of the vaccine wherever public or private experiments were made, must inquire into the results, details of which were never given in sufficient number or precisely enough, must reply to the demands for information, to the fears which preceded an experiment, to the complaints which sometimes followed it. Pasteur carried on almost all this correspondence himself. He must also reply to criticisms and to sly attacks as well as to those of open war. Nor were his adversaries confined to France. Koch and his pupil, Löffler, for example, had published against the theory and practice of vaccination some awkward and fruitless criticisms, which they must regret to-day. In this continual strife, Bouley made himself the champion of Pasteur and devoted his whole spirit to the task.

Thanks to these prodigious efforts, thanks to the precision of the results, the practice of vaccination quickly became the custom, and when publishing, in 1894, in the *Annales de l'Institut Pasteur*, the statistics on anthrax vaccination on sheep and cattle, M. Chamberland was able to state, that in the case of the former a total of 3,400,000 animals had been vaccinated in 10 years with a mortality of less than 1 per cent; in the case of the second, a total of 438,000 had been vaccinated with a mortality of about 3 per thousand. Finally, he estimated the beneficial results for French agriculture from the use of vaccines at 5,000,000 francs for sheep, and 2,000,000 francs for cattle. It is evident that if the laboratory had been laboriously painstaking, it was not labor lost. It is anthrax vaccination that first spread through the public mind faith in the science of microbes.

## V

## STUDIES ON RABIES

Although it was these experiments at Pouilly-le-Fort and the anthrax vaccinations which first overcame the general scepticism regarding the new doctrines, it was the prophylaxis for rabies which gave them the great place in public confidence which they now enjoy. We cannot fail to recognize that, from this point of view, this disease was well chosen. It has, fundamentally, no importance. The mortality which it causes is slight. Man can protect himself from it without any scientific apparatus, simply by police measures, as is done in Germany, and that country may well scoff at us, since without any Institute for fighting rabies, she had less deaths from it throughout the whole empire than we have in Paris. But rabies has a hold on the public imagination; it evokes legendary visions of raging victims, inspiring terror in all those in their vicinity, bound and howling, or asphyxiated between two mattresses.

The reality is much more simple and calm, and few deaths are more peaceful than certain deaths from rabies, but it was easy to foresee that a victory over this disease would be reckoned none the less as a great one. Only it did not seem easy. In the first place, while rabies might pass with the public for a virus disease, it had not that character for the physician or the surgeon, because every man and every animal that contracted it died from it, and it was consequently impossible to know whether it would recur in the same individual. In the second place, the only means of transmitting it was by having a mad animal bite another animal, or by inoculating it with saliva from a rabid animal, but this



PASTEUR STUDYING RABIES  
(From the painting by Edelfelt.)



method of transmission was most uncertain. The incubation period for rabies is extremely variable; it may be some days or it may be several months. Nothing is more unendurable for an experimenter than these long and uncertain delays between an experiment and its results. Moreover, sometimes it happens that the bitten or inoculated animal does not die, and everything has to be done over again. Finally, as a last obstacle, numerous attempts carried on for a long time in the laboratory of Pasteur, and elsewhere, had shown that it was impossible to discover in the saliva of rabid animals any organism having an assured etiological relation to the disease. Pasteur, after having believed that he had discovered it, had renounced this idea, which he had had the prudence not to publish, so that he attacked the question without knowing whether the disease was a virus disease, without knowing or being able to cultivate the microbe, and even without having a certain and quick method of inoculation. It is here that we shall soon see the power of the experimental method when it is handled at the same time with prudence and audacity. It is a marvelous tool, having an extraordinary power of penetration, being able, provided it is handled by one who thoroughly understands it, to work even in obscurity, like those drills which attack and pulverize everything that is presented to them in the depths of a black pit, provided that they are entirely in the grasp of the man who directs them.

The general symptoms of rabies bore witness that it was especially the nerve centers which were attacked. Dr. Duboué, of Pau, had already observed this and concluded that not simply the saliva of a mad animal but also its nerve-substance should be virulent. Experiment has demonstrated the justice of this conclusion. Nerve tissue,

inserted under the skin of an animal, can give it rabies. But this method of transmission is quite as uncertain and capricious as transmission through the saliva. Rabies does not always appear, and it sometimes does so only after a prolonged incubation of months. Inoculation under the skin, therefore, is an uncertain method. But, said some one in the laboratory of Pasteur, why not try to deposit the virus in the nerve centers, since it is there that it grows and reproduces itself.

For that purpose it was not necessary to know the microbe, nor even to be sure that there was one; the proof of its presence and its development would not be microscopical examination, but the appearance of rabies in the animal inoculated. As a culture medium the nerve tissue offers, moreover, guarantees which one does not find either in the saliva or even in the blood, both of which are much more accessible to contamination from the exterior. Furthermore, it seemed to be a chosen medium for the virus of rabies, and to fulfil naturally for it that condition which was the foundation of the culture method, and which was realized only after much labor in the artificial culture media for the anthrax bacteridium and the microbe of chicken cholera. The main thing was to gain access to it properly and to make an antiseptic inoculation there. The surest way was to attempt to inoculate a dog under the dura mater, by trepanning. "Ordinarily an experiment once conceived and talked over was put under way without delay," says Dr. Roux. "This one, on which we were counting so much, was not begun immediately. Pasteur, who had been obliged to sacrifice so many animals in the course of his beneficent studies, felt a veritable repugnance toward vivisection. He was present without too much squeamishness at simple operations, such as a subcutaneous inoculation, and yet, if the animal cried

a little, Pasteur immediately felt pity and lavished on the victim consolation and encouragement which would have been comical if it had not been touching. The thought that the skull of a dog was to be perforated was disagreeable to him; he desired intensely that the experiment should be made, but he dreaded to see it undertaken. I performed it one day in his absence; the next day, when I told him that the intracranial inoculation presented no difficulty, he was moved with pity for the dog: 'Poor beast! His brain is without doubt wounded. He must be paralyzed.' Without replying, I went below to look for the animal and had him brought into the laboratory. Pasteur did not love dogs; but when he saw this one full of life, ferreting curiously about everywhere, he showed the greatest satisfaction and straightway lavished upon him the kindest words. He felt an infinite liking for this dog which had so well endured trepanning, and thus had put to flight for the future all his scruples against it."<sup>1</sup>

The method was in reality discovered. It was that of making pure cultures in the organism. The dog thus trepanned developed rabies in fourteen days, and all the dogs treated in the same fashion behaved similarly. It was now possible to make progress, and from that moment everything went on as in the case of chicken cholera and of anthrax.<sup>2</sup>

For these latter maladies the virulence can be varied by changing the culture medium. Pasteur had likewise discovered, for chicken cholera as well as for anthrax that the virulence varied with the transfer of the microbe from one animal species to another, and we shall soon

<sup>1</sup> L'Œuvre médicale de Pasteur, par M. le Dr. Roux, *Agenda du chimiste*, 1896.

<sup>2</sup> All the studies on rabies are summarized in *Comptes rendus de l'Académie des Sciences*, beginning with 1881. They were done in collaboration with MM. Chamberland, Roux et Thuillier.

re-survey these results and the conclusions which can be drawn from them. In the case of rabies, where cultures could be made only on the living creature, this method was obligatory. He tried, therefore, the inoculation of a rabbit by trepanning and saw that the virus, when thus passed from rabbit to rabbit, was strengthened, and that the duration of the incubation in the end was no more than six days. In the monkey, on the contrary, the virus becomes attenuated. This confirmed the analogies between rabies and the virus diseases.

But if the spinal cord of an animal that has died of rabies can be considered as a pure culture of the virus, why not try to attenuate the virus by allowing a portion of this cord to become old in contact with pure air, as the virus of anthrax is attenuated by exposing a pure culture to pure air. Thus occurred wholly naturally this great discovery that the spinal cord from a rabid animal, exposed to the action of air, in an atmosphere free from humidity, loses its activity on drying. After 14 days, the virus is harmless in the strongest doses; between the fresh cord and that 14 days old, there is a whole series of degrees of attenuation. "A dog that receives this rabic spinal cord 14 days old, then the following day that 13 days old, then that 12 days old, and so on until the fresh cord is used, does not contract rabies and has become immune to it. Inoculated in the eye or the brain with the strongest virus, it remains healthy. It is, therefore, possible in 15 days to give to an animal immunity against rabies. Now men, bitten by mad dogs, ordinarily do not contract the disease until a month or even more after the bite, and this period of incubation can be utilized for rendering the bitten person immune.

"Experiments made on dogs bitten and inoculated were successful beyond all hope. One recalls how, with



the aid of MM. Vulpian and Grancher, the experiments were extended to man. To-day almost 20,000 persons have undergone this antirabic treatment and the mortality occurring among these treated persons has been less than 5 per thousand.

“The discovery of the prophylaxis for rabies aroused everywhere great enthusiasm. It increased the popularity of Pasteur more than all his former works. In return for such a benefaction, the great public desired to manifest its gratitude in a manner worthy of itself and of the man it wished to honor. It was then that the subscription was started which has made possible the founding of the Pasteur Institute.”<sup>1</sup>

Once again the method had brought forth fruit. We could further cite, as proof of its value, the vaccination for erysipelas of swine, preëminent among the workers on which was the regretted Thuillier. But we should find therein only what we already know. We are not writing the history of the work of Pasteur, but that of his mind, and it is better to take up an aspect of the question of viruses which we have not yet considered.

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## VI

### THE PROBLEM OF IMMUNITY

The theoretical importance of all these facts was superior even to their practical importance. This method of the physiological study of microbes in pure cultures which had at first given the etiology of the different diseases studied, which later had furnished all the ideas which we have just summed up on variations in virulence, was about to exhibit a new fecundity by opening up the problem of immunity, on which

<sup>1</sup> Roux, l. c., p. 543.

scientists are still working, and on which the last word has not been said.

On what depends that immunity which vaccinated animals possess, which is also possessed by animals naturally resistant to certain diseases fatal to other species? Why does the cow contract anthrax less easily than the sheep of Beauce, and the sheep of Algiers less easily still than the cow? Why is man not attacked by certain diseases of the domestic animals, and inversely? Here were questions which, yesterday premature and audacious, could now be stated and become the object of an experimental study. In a word, it was not alone the mechanism of the disease which ought to be the subject matter for experiment, but also the mechanism of health, that is to say, the entire physiology of the living creature, and already one could foresee that Pasteur and Claude Bernard were about to join hands to contribute to a deeper conception of the life of the cell.

The new idea which Pasteur brought into this study was the idea of strife between two cells or two groups of cells, and here I seem to be advancing a daring proposition, to such a degree does the idea of strife form a part of the old conception of disease and even, generally, of the appearance of the sick person. During the metaphysical period of pathology, when the direction of life was attributed to a *vital force* superposed on all the organs, one had been led to imagine the disease as a distinct entity, entering into combat with the vital force in the organism.<sup>1</sup> When, through the progress of physiology, the vital force was, so to speak, reduced to an infinite number of cellular lives, each having its

<sup>1</sup> This is the theory of homeopathy. If the proper drug is administered, that is, one having a greater affinity for the entity of the disease than the latter has for the body, then the drug-spirit and the disease-spirit will combine and the patient will return to his normal condition. Vide Hempel's *Materia Medica*. *Trs.*

modality and its direction, it was necessary that the idea of disease also be changed, and we have already seen the efforts made to ascribe physico-chemical origins to pathology. In this conception the old idea of strife had entirely disappeared, and although, for Virchow, a tumor was a physiological development misplaced in time and space, that is to say, produced where it ought not be, and at a time which was not its own, it was difficult to see therein anything which resembled the conception that made the disease something at war with the vital force.

It is for this reason that the physiologists were so opposed to the microbial doctrines. The microbe, producing a chemical phenomenon or causing a disease, was the sudden reappearance of the vital force in regions from which it was desired to eliminate it. The idea of the microbe brought back in the clearest manner the idea of conflict, of strife for the necessities of life, of the struggle for existence. Such is the idea which Pasteur, more than any one else, was instrumental in introducing into science and into pathology.

This idea in its turn underwent some transformations in his mind. At the time of the publication of his *Études sur la maladie des vers à soie*, the microbe was for him a pathogenic cause external to the organism, functioning simply and in some measure irresistibly. In order to be rid of the disease, the parasite must be disposed of. This is what Pasteur had done for the corpuscle of the *pébrine*. It was what had been done before him for the muscardine fungus and the itch mite.

This rather absurd conception of bacterial diseases was for Pasteur in perfect accord with what he then knew of microbes. He believed that the bacterial species were nearly constant in form and possessed immutable properties. Transferred from medium to medium they

would always cause the same reaction, which was a surer means of recognition than their microscopical appearance. Transferred in the same way to a living creature they would produce a definite disease, that is, one which was always the same when the avenue of entrance was the same, and which became thereby a sort of morbid entity: thus bringing us back, in the experimental field, to the oldest conceptions of medicine. Studies on the *flacherie* scarcely modified this point of view. They had shown merely that the microbe, in order to become active, sometimes needed to be aided by external conditions. But when it did act, it always produced the same results.

In short, when nearly 60 years of age, Pasteur discovers facts which are not in accord with this old conception. These relate to the attenuation of virus. One and the same microbial species can invest itself, according to the culture conditions, with characters which render it unrecognizable to one who has not followed it closely through all of its transitions. I have stated above how Pasteur had endeavored to convince himself that there were in his cultures of the septic vibrio two species of unequal virulence, which the culture conditions enabled him to separate. He refused to admit that these culture conditions could produce them. The same may be said of the chicken cholera. It was the struggle between the old spirit and the new, and one must admire the readiness with which Pasteur abandoned his first conceptions when experiment had taught him that they were not in accord with the facts.

It was with ardor and without regret that he threw himself into this new path, divining the resources which he would find there for attacking the greatest and most delicate problems of pathology. He could henceforth take up again his old idea of conflict, no longer that

brutal strife where the only possible means of intervention consisted in the suppression of one of the adversaries, but a gentle strife which one might attempt to direct by augmenting or diminishing the forces of one of the contestants. It was only a question of finding the ground and the object of the strife, and, for that purpose, he had the experimental method: it was possible, working with a single species subject to anthrax, to study bacteridia of different degrees of virulence; it was possible, with the same bacteridium, to study different species, or animals of the same species unequally vaccinated, which made them, to a certain degree, different animals. We see what a field of labor opened before him. It is characteristic of certain discoveries that they suddenly reveal vast horizons. Pasteur had climbed little by little to one of those mountain heights from which a whole new country is visible. He plunges into it with delight. Let us accompany him. We can no longer follow him closely and must abandon the historical order. In the first place, we have reached the latter part of his life and his later conceptions. In the second place, what interests us is the plan of the edifice, and not the order in which its different parts have been erected. If we wish to know which part belongs to Pasteur himself, which part he has built, we must take it in the condition in which Pasteur left it, with its finished parts, with its stones yet unplaced, and with a brief indication of what the progress of science has contributed to it.

## VII

## VIRULENCE AND ATTENUATION

Attenuation is a general phenomenon. After having determined its occurrence in chicken cholera, the anthrax bacteridium, rabies, and the organism of erysipelas of the pig,<sup>1</sup> Pasteur found it in a microbe occurring in horses which had died from typhoid fever, and in another organism derived from the saliva of a child attacked by hydrophobia, which last mentioned organism was found later to be the pneumococcus of Talamon-Fraenkel. All these bacilli became attenuated when they were allowed to *grow old* in the fluid culture medium.

But what do we mean by this expression "grow old"? Age is a result, and cannot be an active cause. It accompanies attenuation, it does not produce it; or, rather, the same cause which produces one, at the same time produces the other. When we search for some physico-chemical influence which might come into play, we think at once of oxygen.

The micrococcus of chicken cholera is, for example, an aërobe in the culture flask and in the organism. When it ceases to multiply in the culture medium, it continues to respire there, to give off carbonic acid by consuming its own tissues. It contracts and shrinks visibly (Fig. 22). Its attenuation, which is a proof of its debility, is probably due to this internal process, and in reality experiment teaches that when the supply of oxygen is limited by sealing the tubes, allowing only a small amount of this gas to be present, the virulence is maintained much longer. It is the same in all cases, and always the oxygen, regarded as the agent of com-

<sup>1</sup> *Fr.* Rouget de porc; *Ger.* Schweinerothlauf. *Trs.*

bustion of the tissues in the absence of food, and consequently as the agent of enervation, is, at the same time, an agent of attenuation. Attenuation and weakening are synonymous, and we have here a conception which harmonizes well with our idea of strife in the microbial diseases. That which is harmful to the microbe is of value to its host.

We are then justified in asking ourselves if all these causes of weakening on the part of the microbe, all these factors which contribute more or less quickly to its death, do not first cause it to pass through a series of successive attenuations, that is, transform it into vaccines. To this new question, experiment replies without hesitation, "Yes." In a general way, attenuation is one of the forms of the gradual weakening of a microbial cell which is on its way to death, and every action harmful to the microbe begins by diminishing its virulence. Such, for example, is heat, too high a degree of which kills the microbe, as we know. Between the optimum temperature for culture and the death point exists a zone of attenuation, observed by M. Toussaint and carefully studied by M. Chauveau, for the anthrax bacteridium. The duration of the heating should be in inverse ratio to the elevation of the temperature and, for a given temperature, directly proportional to the degree of attenuation to be obtained.

Next to the action of heat naturally comes that of the light of the sun. It kills the microbe after a certain length of exposure to it, but before killing, it causes attenuation. This is the conclusion from my experiments, followed by those of M. Arloing.

So much for the physical agents. Now for the chemical ones. Oxygen is a physiological factor of the greatest importance, and we have already examined its rôle in this relation. But it plays also a rôle more

exclusively chemical, a toxic rôle, demonstrated by P. Bert. All microbes require a small amount of oxygen and are injured by an excess of it. The anaërobes must have traces of it but die in ordinary air. The aërobes live in ordinary air but die in compressed oxygen. Between the physiological limits and the toxic limits there is, moreover, a zone of attenuation, studied by M. Chauveau for the anthrax bacteridium.

After oxygen, come naturally the antiseptics which, likewise, when present in very small proportions, are harmless or even beneficial to the microbes, but if present in larger quantities kill them. MM. Chamberland and Roux have studied the action of phenic acid, of bichromate of potash and of sulphuric acid on the anthrax bacteridium and have discovered in this way some curious facts to which we shall soon return.

In short, there are several means of producing from the same virulent race a whole series of races more and more attenuated. Up to this time we have studied them only as *vaccines*. In order fully to investigate their rôle from this new point of view, it is necessary to study them in themselves.

How do bacteridia which are not equally attenuated differ physiologically? They are very much alike in bouillon cultures. When attenuated they produce rods which separate easily and diffuse through the culture medium, clouding it, while the virulent bacteridia adhere in flakes, which float in the midst of a clear liquid. But their physiological needs are the same, and it is almost impossible to differentiate them by means of the microscope. For that purpose they must be inoculated into living creatures.

Let us study them in animals. In proportion as the bacteridium becomes attenuated, we find that it ceases, first, to become virulent for cattle, but that it is still



capable, at this time, of killing sheep; attenuated a little more it ceases to be fatal to sheep, but still kills rabbits and guinea-pigs. When it no longer kills adult guinea-pigs, it still kills young guinea-pigs or young mice. This is also true for other microbes.

Virulence appears to us, therefore, to be an intrinsic quality of which the microbe will be divested more and more until it becomes harmless. But here is a fact which proves that things are not as simple as they seem. If virulence were only this, the different methods of attenuation would destroy it in the same fashion, and the order in which the different species of animals are attacked would be always the same. But experiment shows that this order varies according to the method of attenuation. The anthrax bacteridium attenuated, for example, with bichromate of potash, in the experiments of MM. Chamberland and Roux, as we shall see at once, may still kill the sheep or at least make them very ill, leaving them in the latter case vaccinated, while it produces no effect whatever on rabbits or guinea-pigs, and does not even vaccinate them. It is exactly the reverse of the behavior of the anthrax bacteridium attenuated by growth at  $42^{\circ}$  to  $43^{\circ}$  C., which kills guinea-pigs and rabbits at a stage when it is harmless for the sheep, and does not even vaccinate them. We obtain the same results with *spores* of the anthrax bacteridium attenuated by the action of a temperature of  $35^{\circ}$  C., in a liquid containing 2 per cent sulphuric acid.

Thus virulence is not, as we might suppose, an absolute quality, diminishing little by little after the fashion of reserve food; it is a relative quality, in the estimation of which not only conditions pertaining especially to the microbe must be taken into account, but also those pertaining to the nature, age, and as we shall soon see, the individuality of the animal on which it is studied.

According to our way of looking at things, nothing is less surprising. The word "virulence" sums up the result of the conflict between two organisms. It is necessary, therefore, to take into account the qualities of the two adversaries.

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## VIII

### RETURN TO VIRULENCE

We shall reach the same conclusion by an inverse method, that is, by examining the conditions determining the return of virulence in a microbe which has lost it. We know that these positive and negative variations of virulence may be produced by simple changes in the culture medium, but, from this standpoint, they are of little interest. These variations become interesting only as they manifest themselves in living creatures. Let us see, therefore, if we cannot revive virulence by passage through different species of animals unequally sensitive.

We have obtained, it will be remembered, a strain of the anthrax bacteridium absolutely harmless, then one very much weakened, still able to kill guinea-pigs a day old, but not to kill older guinea-pigs nor other species of animals, then, starting from this one, a whole series of microbes more and more virulent. Can one bring back the most attenuated strains to a state of the highest virulence? Experience replies, "No," in the case of a completely non-virulent anthrax bacteridium, for it escapes our experimentation by refusing to grow in any living organism; it is henceforth fixed, and if it ever returns to virulence, it will be by passing through a new species of animal different from those which hitherto have been shown to be capable of contracting anthrax.

But the case is different for those strains which still

preserve an action on a living species. Let us take for example the most attenuated, that which is barely able to kill a guinea-pig a day old: if we inoculate its blood into a guinea-pig of the same age, that of the second animal into a third, and so on, we shall shortly see the virulence of the bacteridium return little by little. Soon we shall be able to kill with it guinea-pigs three or four days old, a week, a month old, and finally sheep. By successive cultures in living media, the bacteridium has been restored to its original virulence.

It is justifiable to form out of these facts a general rule, in accordance with our theory. A microbe introduced into the body of an animal is not living under the same conditions as one sown in an inert vessel; it is subjected to the pressing alternative of living or dying, of being victorious or vanquished. Vanquished, its history is soon written; victorious, it will come out of the struggle strengthened, that is to say, having complied with the conditions of its new medium, it is better prepared to accommodate itself therein anew. If it is transferred several times from individual to individual of the same race, without having been influenced by external conditions in the interim between two passages, we may expect to see its virulence augmented and in some degree fixed for the race and for the customary mode of transmission in this race. Thus the bacteridium of sheep anthrax, for example, living for a long time on our soil, is acclimated to some degree in the race which shelters it, and its virulence varies little from one subject to another, and from one year to another for the same country. The same thing is true, to a certain extent, for Jenner's vaccine, if it is transferred directly from arm to arm on unvaccinated healthy individuals, and if it is carefully preserved between the two operations. The same thing is also true for the virus of rabies administered by tre-

panning, after a certain number of passages through individuals of the same species.

Having once attained this stability, which is not its maximum virulence for the race, as we shall see later, the virus preserves this degree of virulence practically unchanged, if the paths of penetration do not vary. This increased virulence may permit it to invade another race or another species. Thus our anthrax bacteridium, invigorated by a passage through the guinea-pig, can infect the sheep. But there may also be produced cases analogous to those in the experiments of MM. Chamberland and Roux, in which the virulence augmented for one species will be diminished for another, or inversely, and we reach a third possible case, that of the diminution of virulence for one species by passages through another species.

We shall find an example of this fact, so clear that it is almost diagrammatic, in the work of Pasteur and Thuillier, on the erysipelas of the pig. This disease is due to the development in the tissues of the animal of a very short and slender rod. It goes through its stages of evolution very rapidly, and may cause death in some hours.

It is not confined to swine, but may also be communicated to the pigeon and the rabbit. If there is injected into the pectoral muscles of a pigeon the microbe of the erysipelas taken from a diseased pig, or from a culture in veal bouillon, the pigeon dies in from 6 to 8 days, after having shown the external symptoms and the somnolence of chicken cholera. We might believe that the two diseases are identical if the organism of the erysipelas were not absolutely harmless to the chicken, which is so sensitive to the action of the cholera microbe.

If the blood of the first pigeon is injected into a second, the blood of the second into a third, and so on, the malady

becomes acclimated in the pigeon, makes it sick and somnolent more quickly, kills it sooner, and the blood of the last pigeon injected into the pig, manifests there a virulence superior to that of the most infectious material from a pig which has died of erysipelas, even if the pig was naturally infected. Here we have then augmentation of virulence for the pig by passing the organism through the pigeon. The maximum to which a virus can attain by passage through a race is, therefore, not always, the maximum for that race.

There we have a case of augmentation, here is a case of attenuation to which I wish especially to call attention. Let us substitute the rabbit for the pigeon in this series of experiments. The microbe becomes accustomed to the rabbit; all the animals die, but if we inoculate pigs with the blood of the last rabbits for comparison with that taken from the first rabbits in the series, we find a progressive diminution of virulence. Soon the blood of rabbits, inoculated into pigs, no longer kills them; it only makes them sick and leaves them vaccinated against the fatal erysipelas. Entirely parallel facts have been worked out with other microbes. They furnish a method of attenuation of viruses by passages through living species, and increase our means of action in a field of studies the future of which will show its astonishing fruitfulness.<sup>1</sup>

We have now come back, apparently, to a conclusion already stated: *Virulence is a state of perpetual becoming.* But how much we have developed this idea, and what precision the new facts have given to it, and to the bond of theory which has enabled us to unite them! In the

<sup>1</sup>This prediction has been more than fulfilled. Since this book was written very wonderful advances have been made in bacterio-therapy, the most striking of which have been the control of diphtheria and the prevention of typhoid fever and of tetanus. *Trs.*

beginning we ascribed variations in virulence to the microbe itself and there was there a vast field for evolutions, but it did not embrace all the possible ones. We have been obliged to add to it those which come from the variation of the living organisms in which the microbes establish themselves, and the virulence which we see results from an infinite number of combinations of these two causes of variation.

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## IX

### CHEMICAL AND HUMORAL THEORIES OF IMMUNITY

From what we have just said it follows that the word virulence has no meaning either in relation to the microbe or to the host. It signifies little more than the relation between strength and resistance, without telling us anything about the absolute value of these two forces. A microbe which does not kill a given animal or does not make it ill is devoid of virulence with respect to that animal, and one might believe from this statement that all the truths which we have discovered are naïvetés, or mere definitions of words; that would be making a great mistake. What we have discovered, in reality, is a new field of study. With respect to this or that animal, such or such a microbe may remain harmless for many reasons. It cannot develop in its tissues, or, if it does develop, deposits there no injurious substances, or even, perhaps, produces beneficial effects, leading to increased resistance. The field of hypotheses is unlimited. Let us see what experience offers, and let us observe how much the field of experiment has been extended, thanks to Pasteur.

Here are normal sheep inoculated, some with the

virulent bacteridium, others with the attenuated bacteridium. The first develops and kills the sheep. The second, after a period of growth made with more or less difficulty and causing a transitory illness of the sheep, abandons the struggle and leaves the animal more or less vaccinated. This is one method of studying the influence of the bacteridium alone.

Now let us take a normal sheep and a vaccinated sheep, into which we inoculate a very virulent strain of the anthrax bacteridium. It kills the first and has no effect on the second. Here we have a way to study the influence of immunity acquired by a former vaccination.

Let us take now a French sheep and an Algerian sheep; let us inoculate both of them with a light dose of a virulent strain of the bacteridium. The first will die, the second will resist, after an illness in general benign. In this we have the influence of race or of natural immunity.

The French sheep has a natural immunity for the attenuated bacteridium; the Algerian sheep, a natural immunity against the virulent disease; the vaccinated sheep an acquired immunity, more or less marked; the dog, a natural and absolute immunity. In all the cases, the natural or acquired immunity, when it is complete, is correlative with the non-development of the bacteridium, which instead of invading the tissues, remains confined to the point of inoculation or its vicinity, and finally perishes there.

What is the cause of this non-development of a living cell which has been sown? This question is what the inquiry led to! We see that it was precise. It was already a conquest only to be able to state it thus. Until that time it had been necessary to bow down without seeking to penetrate the mystery. What reply, in fact, can be given to this general question: Why is the sheep sensitive to anthrax, and the dog not sensitive? Why

is man alone able to contract syphilis?<sup>1</sup> These are questions which one did not even dream of putting to himself. But after living viruses were discovered and their conditions of growth were known, man could ask himself why they develop here and not there, on the French sheep and not on the Algerian sheep, both of which are, however, authentic sheep.

For an answer to this embarrassing question, Pasteur sought quite naturally, as any man of science would do, in his experience and memory. They were, it is true, the experience and the memory of a chemist, and the question did not remain long in the field where he first placed it. But all theory is good which foresees new facts, and however inexact it appears to-day, the explanation of Pasteur has had that merit.

He knew, through his long experience with fermentations, that even when one works *in vitro* the smallest circumstances suffice to permit or to hinder the development of a microbe. When he saw certain of them demand veal-bouillon and certain others fowl-bouillon, it did not surprise him that a particular disease was peculiar to a particular species, and another disease to another species. Neither was it astonishing, knowing how hard to please the microbes are on questions of temperature, that the chilled fowl should contract anthrax, while at its ordinary temperature it remained unaffected. Finally, knowing, as we have said, that the chicken cholera microbe refuses to develop again in a medium in which it has already lived, why be astonished that it should refuse to live again in an organism which it has already invaded? There was, in these exclusively physical or chemical

<sup>1</sup> We now know from the studies of Metchnikoff that syphilis is inoculable into apes, and from those of Noguchi into rabbits the living testicles of which are the best culture medium for the propagation of the *Treponema pallidum*—the protozoan cause of syphilis. *Trs.*



facts, a wholly natural explanation of the non-recurrence of virus diseases.

Let us investigate in this direction. Why does not the same bouillon culture nourish easily a second time the species which has already lived in it? The failure might result from one of two things: either the organism removed from the bouillon the first time a substance needed in its development, or else it deposited in it an injurious substance.

Pasteur and his colleagues inclined toward the first explanation. M. Chauveau, on the contrary, favored the second and supported it on two arguments of unequal value. He was of the opinion, for instance, that the vaccination of the foetus by the mother, that is to say, the transmission of immunity through the placenta, which he had often had occasion to verify in anthrax, and which MM. Arloing, Cornevin and Thomas had just proved for the symptomatic anthrax, was better explained by the introduction of an injurious substance into the blood of the foetus, than by the disappearance of a needed substance. The two bloods of the mother and of the foetus being constantly in position to exchange chemical substances, are likewise in position to lose or to acquire, and there appear to be no reasons for believing that preference is given one over the other. Another argument of M. Chauveau was worth more. He called attention to the curious influence of the quantity of virus used in inoculation. The Algerian sheep is immune to doses which kill the French sheep, but, if we increase the dose, we also kill the Algerian sheep. If it is much diminished, the French sheep resists in its turn, experiencing only an illness, from which it emerges vaccinated. This is not explained by the hypothesis of Pasteur. If there is lacking in the sheep an element needful for the multiplication of the bacteridium, we

do not understand why its absence no longer interferes with growth when the number of microbes increase which have need of it for their development. On the contrary, it is much more comprehensible why the presence of an injurious substance can stop a small detachment of the enemy, and not a large troop.

It is useless to dwell upon the discussion of these explanations of immunity, both of which may indeed have their part in the phenomenon, but cannot play a stellar rôle. Strictly speaking, they are sufficient to explain the immunity produced by vaccination, but they weaken when it is a question of explaining the duration of immunity. How can we admit the persistence for years of this injurious element, or the absence of the necessary element, when nutrition and destructive metabolism bring and remove such varied elements. The element *duration* is represented in the tissues, not by the chemical substances which compose them, but by their permanent form—by the cell.

The two explanations which we have just considered are not the only ones which have been proposed. There have been successively attributed to the humors, and to the liquids of the animal economy, a destructive power for microbes, an attenuating power, an antitoxic power, all these powers depending solely on conditions of the physico-chemical order. Without entering into a detail which however important it is, would be out of place here, it can be said that all these theories have shown themselves to be powerless to explain the great fact of the creation and the persistence of immunity. As to the creation of this property in the individual, either it has been found that the liquids in circulation or the humors that occur in the interior of the body, did not have the destructive, attenuating, or antitoxic power which we find in them outside of the organism,

or else if they did have these powers, they were without apparent relation to the resistant or vaccinated state of the animal. For the conservation of immunity, the same criticisms apply as to the theories of Pasteur and Chauveau. A chemical action, whatever it may be, cannot be lasting in an organism in which all the chemical elements are constantly being renewed. There is only the cell which lasts, because it lives. It is more likely that the explanation of immunity lies in the cellular theories than in the humoral theories which we have just briefly reviewed.

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## X

### CELLULAR THEORY OF IMMUNITY

Pasteur, who in his heart was indifferent to theories and asked of them only that they suggest experiments to him, held for a long time a purely cellular conception of microbial disease. It was by a struggle between the red blood corpuscles and the bacteridium that he explained in 1878 the resistance of the living fowl to anthrax, and we see him at every instant, in that period, having recourse to vital resistance, and saying: "Among the lower forms of life, still more than in the higher species of plants and animals, life prevents life." Again, it was this same sentiment which guided him in the experiments which we have seen him making, to prevent the development of the anthrax bacteridium by inoculating at the same time with some common bacteria. Pasteur, however, was conscious of not having laid hold of the vital point of the mechanism of the resistance of the organism, and it is perhaps for that reason that when he heard of the researches of Metchnikoff on phagocytosis, he gave

immediate attention to them. It is his letter, inserted in the first number of the *Annales de l'Institut Pasteur*, which first pointed out to the French public the researches of M. Metchnikoff.

The simplicity of this conception was striking. These white corpuscles of the blood and of the tissues, playing the rôle of gendarmes in the organism, constantly in circulation, always ready to throw themselves on everything foreign appearing there, and consequently upon enemies living or dead, surrounding by virtue of this general property the cells of the microbes, digesting them and making them disappear—all that could not fail to captivate him! The idea was the idea of a biologist and of a naturalist; it had not occurred to Pasteur, but that did not prevent him from welcoming it with deference. As long as he lived, he wished to keep in touch with its progress.

It pleased him so much the more that after remaining for some time in the field of anatomy and natural history, the problem was not long in returning to the field of chemistry, to which all our conceptions, whatever may be their objects, provided they are deep, are not slow in returning, because, at bottom, it is chemical mutations which govern everything.

The theory of Metchnikoff had, moreover, for his mind, this satisfying side that it equalized the competitive forces. There is something disproportionate in a bacteridium which kills an ox. One understands better a localized struggle between the leucocytes of the ox and the invading microbes, which perish if they are too feeble, or too few in number, but which take possession of everything if they are the stronger, because they have the power of multiplication in their favor.

Nevertheless, thus limited and defined, the conditions of the struggle remained hazy and somewhat mysterious.

One might have understood a conflict between the microbe and the cells directly reached by the inoculation or located in its neighborhood; but obedient to what mysterious call do the white cells come from all parts of the organism, filtering through vessels, and penetrating to the region where they will be useful? The living cells have no emotion, not even that of well-being, they have only needs, and obey only physical or chemical actions.

The discovery of chemiotaxis, and the extension to the leucocytes of ideas introduced into science by Pfeiffer has taken away from the theory of M. Metchnikoff a little of its mysterious aspect, and with the same stroke has brought back to the field of chemistry the question which had been referred to the cellular field. It demonstrates the existence in the leucocyte of a sort of *far-away scent*, which indicates to it the directions in which it will find substances suited to its taste, or from which it can derive benefit. These substances are secreted by the microbes used for inoculation, or introduced with them in the bouillon cultures. Immediately, they challenge the enemy and the struggle begins. It can happen, and in fact does happen sometimes that the secretions of the bacillus are not inciting, and even that they are repellent. Then the bacillus protects itself against the leucocytes, and can develop at its ease, if the host does not put into play secondary causes of resistance.

As to the struggle, when once begun, its issue always rests undecided *a priori*. Sometimes the leucocyte, surrounds the microbe and digests it. It becomes a *phagocyte*. Sometimes also the ingested microbe succeeds in remaining alive, continues to secrete injurious substances, a toxine, and it is the leucocyte which succumbs. In cases in which disease follows the inoculation, the victory remains undecided for some time, then results in favor of one of the adversaries.

When it is the host which succumbs, the microbe seems to emerge more inured to the struggle, capable of secreting in greater abundance the products which have rendered it victorious. We explain this fact by saying that it has become more virulent, and a good way of increasing its virulence is to make it pass through species, which without being absolutely immune, can resist it a long time and enable it to acquire a new vigor. That is what we did when we rendered the anthrax bacteridium more virulent by making it pass through species more and more resistant to its action.

On the other hand, when it is the microbe which succumbs in the struggle, the leucocytes in their turn issue from the conflict stronger, more sensitive to the chemiotaxis of the microbes which they have killed, and more accustomed to their toxins, and the animal consequently has a power of resistance, an immunity, which it did not formerly possess.

It is not necessary to enter into details to see that we have here a conception which lends itself in a remarkable manner to the interpretation of all the very curious facts discovered by Pasteur. I add that this interpretation is not purely theoretical. It is sufficient to read, in the *Annales de l'Institut Pasteur*, the numerous works accumulated on this subject by M. Metchnikoff and his pupils, to be convinced that we are face to face not only with a captivating theory, but with a theory true to its smallest details, and in all respects fruitful.

In résumé, the resistance of each living being with respect to a microbial inoculation is at the same time a question of species, a question of individuals, a question of place and of time, a question of quantity of inoculating material, and also a question of temperature, for a lowering of temperature can diminish the activity of the leucocytes and increase that of the bacillus, as in case

of the chicken which, when chilled, contracted anthrax. A microbe may be harmless for the species which carries it, and may not be so for others, the resistance of which is not organized in the same fashion. It will be understood that it may be fatal to the young animal, whose phagocytes are not inured, that it may develop where the phagocytes are not numerous, and not where it finds them in great numbers and better trained, etc. And all this happens through the intermediary of cellular secretions, that is to say through physico-chemical agencies. It is evident that Claude Bernard and the physiologists who feared to see Pasteur re-introduce into science the idea of life as a hidden cause had in him not an enemy of their doctrines, but a powerful ally. We see also that the physicians were right in treating him as a chemist. They were wrong only in pronouncing this name with a disdainful air. With Pasteur chemistry took possession of medicine and we can foresee that it will not relinquish its hold.









PASTEUR

(Photo. by the writer, from a bronze plaque by G. Prud'homme.)  
(Courtesy of Col. J. F. Siler, Office of the Surgeon General,  
Washington, D. C.)

## ANNOTATED LIST OF PERSONS MENTIONED IN THIS BOOK

[The following statements have been derived principally from French, Italian, and German sources. In a few instances I have taken dates from Garrison's "History of Medicine" (W. B. Saunders Co., 2d edition, 1917). This book contains an appendix entitled "Medical Chronology," very useful to students in fixing dates of various important discoveries in pathology and bacteriology. It contains also portraits of many of the persons here mentioned, and to these portraits I have referred as "Garrison, p. —." The book is very readable and is recommended to all students, even those not interested in medicine. They cannot read it without becoming so. The other abbreviated portrait references, not self-explanatory, are of Pagel's very interesting "Biographisches Lexikon hervorragender Ärzte des neunzehnten Jahrhunderts," Berlin and Vienna, 1901, referred to as "Pagel, p. —," Werckmeister's "Das neunzehnte Jahrhundert in Bildnissen," 5 vols. (1898–1901), Berlin, Photog. Gesellschaft, referred to as "Werckmeister, p. —," Veit Brecher Wittrock's *Catalogus illustratus iconothecæ botanicæ horti Bergiani Stockholmiensis*, Pars I and II. *Acta Horti Bergiani*. Bd. 3. Nos. 2 and 3, Stockholm, 1903 and 1905, referred to as "Wittrock I, or II, Tafl. —" and "Histoire illustrée de la Littérature Française Précis Méthodique." Par E. Abry, C. Audic, P. Crouzet. 3<sup>e</sup> Edition revue et corrigé. Paris. Henri Didier, Éditeur. 1916, pp. XII, 664. A copiously illustrated, inexpensive and fascinating beginner's book of French literature, referred to as "Abry p. —."]

**Appert, Émile** (—— — ——). French mathematician and chemist. First science teacher of Duclaux.

**Appert, François** (17— — 1840). French manufacturer. Brother of the philanthropist. Invented canning for the preservation of foods. Received 12,000 francs from the French Government for making public his discovery. His book (1810) entitled "Le livre de tous les ménages, ou l'art de conserver pendant plusieurs années toutes les substances animales et végétales," passed through five editions.

**Arloing, Saturnin** (1846–1911). French physician and veterinarian. Professor of experimental medicine at Lyons. Studied symptomatic anthrax with Cornevin and Thomas. Investigated peripneumonia, etc. Wrote an "Anatomy of domestic animals" which passed through four editions.

**Bacon, Francis Lord Verulam** (1561–1623). English judge and natural philosopher. His "Novum Organum" was published in London in 1620.

"The wisest, brightest, meanest of mankind." (Pope.)

- Bail, Karl Adolph Emmo Theodor** (1833 - —). German mycologist. Discovered the submerged yeast form of *Mucor mucedo*.
- Balard, Antoine Jérôme** (1802–1876). French chemist. Born in Montpellier. Professor in the Normal School, the College of France and the Sorbonne. Inspector general of higher education. Member of the Academy of Sciences. Discovered bromine (1826) and succeeded in extracting sodium sulphate from sea water.  
 “Par sa chaleur d’âme, il entraîna tout le monde dans un mouvement généreux. C’était un éveilléur d’activités. . . . Ce qui me charmait en lui, c’est qu’il avait le culte de la science pure. Dès qu’un homme de laboratoire mêle à ses travaux d’autres préoccupations, il est arrêté dans sa marche.” (Pasteur.)
- Barbet** (— - —). Director of the “Maison Barbet,” a Parisian preparatory school. Teacher of Pasteur and of Duclaux.
- Bastian, Henry Charlton** (1837–1915). English physician, physiologist and pathologist. Born in Cornwall. Professor in University of London. Member of the Royal Society. Bastian wrote “The Modes of Origin of Lowest Organisms” (1871), “The Beginnings of Life” (1872), and “Studies in Heterogenesis” (1901). Student of nematodes and of the brain and nervous system. Adversary of Pasteur. For portrait see Pop. Sci. Monthly, Nov., 1875.
- Beal, William James** (1833 - —). American botanist. Born in Michigan. Student of Louis Agassiz and of Asa Gray. For many years professor in Michigan Agricultural College.
- Béchamp, Pierre Jacques Antoine** (1816–1908). French physician. Professor in Faculty of Medicine in Montpellier and afterward in the Catholic Faculty in Lille. Antagonist of Pasteur. Copious writer. His chief work is “Les Microzymas dans leurs rapports avec l’hétérogénie, l’histogénie, la physiologie et la pathologie, examen de la panspermie atmosphérique continue ou discontinue, morbifère ou non morbifère,” 8 vo., pp. 992, Paris (1883); see also “Microzymas et Microbes” (1888).  
 “As to the nature of the disease [flacherie] and its cause, M. Béchamp ascribes it to mobile molecules which he calls *microzymas* and which he sees swarming everywhere ‘on the surface of the worms, in their fluids, in the eggs, etc.’ I leave to M. Béchamp the complete priority of these facts.” (Pasteur.)
- Becher, Johann Joachim** (1635–1682). German chemist and political economist. A forerunner of Stahl. Helped to introduce potato-culture into Germany—a vast undertaking, since there was a strong popular prejudice to be overcome.
- Beethoven, Ludwig van** (1770–1827). Greatest of composers. Son of a drunkard who was a mediocre musician and of a tuberculous woman who was the daughter of a cook. Generally reckoned as a German,

- but his masque shows Slavie features. He was born in Bonn on the Rhine. His father's father came from the low countries (Antwerp), and his mother's maiden name was Maria Magdalena Kewerich. He was an upright, democratic man, passionately fond of nature and what is best in music, literature and art. He wrote German badly, but in music he was a god! He spent most of his mature life in Vienna and died there. For portraits see "Beethoven" by Vincent d'Indy in "Les Musiciens Célèbres" Paris, Renouard, and "Beethoven, the man and the artist as revealed in his own words," by Fr. Kerst (Tr. by Krehbiel. N. Y., B. W. Huebsch, but without the portraits).
- Bellamy,**
- Bellotti, Cristoforo** (—— - ——). Italian student of silk-worm diseases in the Museo Civico of Milan. Published several papers in Milan (1863-1879). Wrote also on the fossil fish of Lombardy.
- Berkeley, Rev. Miles Joseph** (1803-1889). English microscopist and cryptogamic botanist. Author of "British Fungi," "Decades of Fungi," "Introduction to Cryptogamic Botany," "Handbook of British Mosses," etc. Wrote also on diseases of plants for "The Gardeners' Chronicle." For portraits see Wittrock II, Tafel. 145, and Whetzel's History of Phytopathology, p. 56.
- Bernard, Claude** (1813-1878). Distinguished French physiologist. Magendie's assistant. Professor in Paris. Member of the Academy of Sciences and of the Académie Française. Senator. Discovered action of the pancreas in the digestion of fat, storage of glycogen in the liver, existence of nervous centers acting independently of the brain and cord (sympathetic system), and sugar in the urine as a result of wounding the fourth ventricle of the brain. Author of many books and papers. His "Leçons sur les phénomènes de la vie commune aux animaux et aux végétaux" appeared in Paris in 1879. For portraits see Garrison, p. 576, Pagel, p. 147, Abry, p. 589 and Pop. Sci. Monthly, Oct. 1878.
- Bert, Paul** (1833-1886). French politician (Republican) and physiologist. Student of Claude Bernard. Professor in Bordeaux and in Paris. Received 20,000 francs reward for barometric investigations in relation to life processes. Member of Gambetta's ministry. Pasteur's friend. Wrote "Leçons sur la physiologie comparée de la respiration," Svo, pp. xxxv, 588. Paris, 1870. Dedicated to Claude Bernard. For portraits see Harper's Mag., 1882, p. 560, and Pop. Sci. Monthly, July, 1888. .
- Berthelot, Marcelin Pierre Eugene** (1827-1907). French chemist. Senator. Remarkable for his studies of organic substances: polyatomic alcohols; synthesis of organic substances; thermochemistry; explosives. Assistant of Balard. Professor in School of

Pharmacy and College of France. Member of the Institute. Author of many books and papers. His "La synthèse chimique" passed through eight editions. For portraits see McClure's Magazine, 1894, p. 305, and Pop. Sci. Monthly, May, 1885.

**Bertin, Pierre Augustin** (1818-1884). French physicist. Student in the Normal School. Professor in Strassburg. Professor in the Normal School: master of conferences and sub-director. Friend of Pasteur. For portrait see "Le Centenaire de l'École normale." Paris, 1895, p. 400.

**Berzelius, John Jacob** (1779-1848). Swedish physician and chemist. Professor in Stockholm. Introduced symbolic notation, determined atomic weights, developed the doctrine of valency. Studied and developed electrolysis: in the decomposition of water showed that hydrogen, metals and alkalis go to the negative pole, and oxygen and acids to the positive pole of the battery. Discovered selenium and cerium; showed calcium, barium, strontium, tantalum, silicon and zirconium to be elements; investigated whole classes of compounds. Author of many papers and books, including an annual review of the progress of chemistry and mineralogy for 27 years. One of the fathers of modern chemistry. For portrait see Harper's Mag., 1897, vol. 95, p. 756.

**Biot, Jean-Baptiste** (1774-1862). French physicist, mathematician and astronomer. His chief contributions were in optics. Associate of Gay-Lussac and Arago. A brave and just man. Very helpful to the young Pasteur. For portraits see L'Art, 1876, p. 183, Art and Letters, 1881, p. 187, and Harper's Mag., 1897, p. 49.

**Black, Joseph** (1728-1799). Scotch chemist. Professor in Edinburgh. Foreign member of the French Academy of Sciences. A forerunner of Cavendish and Priestley. Studied alkalis and alkaline earths. Discovered latent heat and "fixed air" (carbon dioxide). One of the creators of modern chemistry. For portrait see Garrison, p. 323.

**Blanchard, Émile** (1820-1900). French naturalist. Professor in the National Agronomic Institute. President of the Academy of Sciences in 1881. Wrote a natural history of insects, etc.

**Bloch, Gustave** (1848 - —). French historian. Professor in Besançon, Lyons and Paris. Officer of the Legion of Honor. French normal school graduate. Eulogist of Duclaux.

**Bornet, Jean Baptiste Edouard** (1828-1912). French algologist. Member of the Academy of Sciences. Contributed much to our knowledge of red algae and lichens. Collaborated for many years with Thuret. For portraits see Wittrock I, Taf. 33, and Wittrock II, Taf. 83.

- Bouley, Henri** (1814–1885). French veterinarian and comparative pathologist. Member of the Institute. President of the Academy of Sciences in 1885. Champion of Pasteur. For a portrait see *Rec. Méd. Vét.*, 7 sér., Tome II, No. 23, 15 déc., 1885.
- Boullay, Polydore** (1806–1835). French chemist. Wrote "Mémoire sur la formation de l'éther sulfurique" (1827), "Mémoire sur les éthers composés" (1828).
- Boussingault, Jean Baptiste Joseph Dieudonné** (1802–1887). French anaeytical and agricultural chemist. Fought under Bolivar in South America. Climbed Chimborazo (1831). Professor in Lyons and in Paris. Member of the Academy of Sciences; Member of the National Assembly (1848). Grand officer of the Legion of Honor. He showed that ordinary plants cannot assimilate free nitrogen. One of the founders of the Science of Agronomy (see his "Traité d'Économie rurale" and his "Agronomie, chimie agricole, et physiologie"). For portraits see Wittrock II, Tafel. 58, and *Pop. Sci. Monthly*, Oct., 1888.
- Boutron, Charlard Antoine François** (1796–1878). French chemist.
- Boyle, Robert** (1627–1691). English chemist and physicist. Brother of the statesman. Discovered Boyle's law. Wrote his "Sceptical chymist" in 1661. Used vegetable colors for determining acidity and alkalinity of solutions; invented a freezing mixture. Founded a lectureship on the Evidences of Christianity. For portrait see *Pop. Sci. Monthly*, Feb., 1893.
- Brauell, J. Fr.** (— — —). German veterinarian at Dorpat. Brauell's first communication appears to have been in Virchow's *Archiv*, 1857. Wrote also on rinderpest (1862).
- Bremer, Gustav Jacob Wilhelm** (1847–1909). Dutch chemist. Taught in Rotterdam. Published in Dutch a paper on malic acid (*Een rechtsdraaiend appelzuur*) in 1875.
- Broussais, François Joseph Victor** (1772–1838). French physician and pathologist. Founder of a school of medicine called "the physiological school," which for a time had an enormous following in France. Broussais was a great believer in the value of starvation and blood-letting. He would cover a patient with leeches. For portraits see Garrison, p. 416, and Pagel, p. 29.
- Brücke, Ernst Wilhelm Ritter von** (1819–1892). German anatomist and physiologist. Professor in Koenigsberg and Vienna. Author of numerous papers on physiology of speech, physiology of colors, etc. For portraits see Garrison, p. 489, and Pagel, p. 259.
- Buffon, George Louis Leclerc de** (1707–1788). French naturalist. Celebrated for the style of his books, which were translated into many languages but are of slight value now. It was he who said:

- "Le style est l'homme même." For portraits see Abry, p. 387 and Petit Larousse illustré, p. 1193.
- Burdon-Sanderson, Sir John Scott** (1828-1905). English physician and physiologist. Lecturer at St. Mary's Hospital. Professor in London University and University College of London. Member of the English Rabies Commission (1886).
- Cagniard-Latour** (or de la Tour) (1777-1859). French physicist. Invented the siren whistle (1809), called in French *cagniardelle*.
- Cantani, Arnaldo** (1837-1893). Italian physician, clinician and pathologist. Son of a Neapolitan physician. Senator. Professor in Pavia and then in University of Naples. Author of several books. Interested especially in infectious diseases. Wrote on cholera. For portrait see Pagel, p. 303.
- Cantoni, Gaetano** (1815-1887). Italian student of silkworm diseases. Professor in the Royal Museum in Turin. Founder and director of the High School of Agriculture in Milan. Author of many books and papers on agricultural subjects. Wrote "Trattato completo teorico-pratico di agricoltura," 3d ed., 2 vols., Milan, 1884-5.
- Chamberland, Charles Edouard** (1851-1908). French physicist, pathologist and bacteriologist. Normal school graduate. One of Pasteur's collaborators. Member of the Legion of Honor. Collaborated also with Roux, Joubert, Strauss, Fernbach and Jouan. Elected radical Republican Deputy from the Jura in 1885. Author of several independent works: "Origin and Development of Microscopic Organisms" (1879), "Drinking Waters and Epidemic Diseases." Invented the Chamberland filter (1884). For portrait see "Ann. d l'Inst. Pasteur," May, 1908.
- Chantemesse, André** (1851 - —). French physician. Professor in the Faculty of Medicine. Officer of the Legion of Honor. Author of "Mosquitos and Yellow Fever," "Flies and Cholera," "Traité d'hygiène," etc. Collaborated in anti-rabies inoculations at Pasteur Institute. One of the Editors of "Ann. de l'Inst. Pasteur."
- Charrin, Albert** (1857-1907). French physician. One of the discoverers of the glanders bacillus (Bouehard, Capitan et Charrin, "C. R. Acad. d. Sci.," Dec. 26, 1882). Collaborated in anti-rabies inoculations at Pasteur Institute. Author of "Les defenses naturelles de l'organisme" (Paris, 1898).
- Chassang, Alexis** (1827-1888). French grammarian, lexicographer and litterateur. Author of many books—grammars, dictionaries, anthologies.
- Chauveau, Jean Baptiste Auguste** (1827-1917). Distinguished French veterinarian, anatomist, physiologist and pathologist. Commander of the Legion of Honor. Member of the Academy of Sciences and of



- the Academy of Medicine. Editor of the "Journal de Physiologie et de Pathologie Générale" and "La Revue de la Tuberculose." Author of the classical "Traité d'anatomie descriptive des animaux domestiques." For portraits see "The Veterinary Journal," London, vol. 73, No. 2, Feb., 1917. "Journal de Physiol. et de Path. Générale." Tome XVII, No. 1. Paris, 1917, and "Recueil de Médecine Vétérinaire," Tome XCIII. Nos. 1-2, Paris. 1917.
- Cohn, Ferdinand Julius** (1828-1898). German botanist. Professor in Breslau. Studied mostly the morphology and developmental history of algæ, fungi and bacteria. Born and died in Breslau. For portrait in age see "Bact. in Rel. to Plant Diseases," Carnegie Inst. of Washington, vol. I, (Frontispiece) and at 33, Wittrock II, Taf. 84.
- Collin,**
- Columella, Lucius Junius Moderatus.** Roman poet of the First Century. Wrote "De re rustica" (12 books in daetylic hexameters).
- Cornalia, Ser Emilio** (1824-1882). Italian zoologist. Student of silkworm diseases. Wrote a monograph on the Bombyx of the mulberry (Milan, 1856). Discovered "Cornalia bodies" (*Nosema bombycis* Nägeli, *Panhistophyton ovale* Lebert), cause of pébrine. Wrote also on geology.
- Cornevin, Charles Ernest** (1846-1897). French pathologist. Student of symptomatic anthrax with Arloing and Thomas. Wrote also on "rouget," and a book on poisonous plants (Paris, 1893).
- Coze, Léon** (1817-1896). French pathologist.
- Darwin, Charles Robert** (1809-1882). English naturalist. A great, simple-minded, humble and lovable man. Probably the most influential person in the nineteenth century. His greatest book "The Origin of Species by Means of Natural Selection" was published in 1859. For portraits see Wittrock II, Taf. 65, Garrison, p. 540, Pagel, p. 33, and Pop. Sci. Monthly, Feb., 1873, and Nov., 1901.
- Davaine, Casmir Joseph** (1812-1882). Illustrious French physician, zoologist and pathologist. Student of anthrax. Member of the Academy of Medicine. Author of a "Traité des entozoaires et des maladies vermineuses de l'homme et des animaux domestiques" (2d ed., 8 vo., Paris, 1878). For portrait see "Arch. d. Parasit.," T. 7, p. 123.
- Dechambre, Amédée** (1812-1886). French physician. Member of the Academy of Medicine. Chevalier of the Legion of Honor. Wrote on "Diseases of Old Age," etc. His vast "Diet. encycl. des Sci. Médicales" (1864-90) includes 100 volumes.
- Déclat, Gilbert** (1827-1896). French physician. Following Pasteur's studies on fermentation he made early use of antiseptics in medicine

and surgery. Edited from 1874 a journal for the diffusion of his ideas called "Médecine des ferments."

**Delafond, Onésime** (1805–1861). French veterinarian. Professor in the school at Alfort. Member of the Academy of Medicine. Delafond was appointed to study anthrax in sheep in 1841. His "Traité sur les maladies du sang des bêtes à laine" was published in Paris in 1845. His second book "Traité sur la maladie du sang des bêtes bovines" appeared in 1848. Delafond's anthrax paper of 1860 referred to in the text, is in "Recueil de Méd. Vétér.," 1860, p. 735.

**Delafosse, Gabriel** (1796–1878). French mineralogist and crystallographer. Pupil of Haüy. Pasteur's teacher in the Normal School. Member of the Academy of Sciences.

"Un homme qui avait le don de l'enseignement." (Pasteur.)

**Descartes, René or Renatus Cartesius** (1596–1650). Distinguished French geometer, physicist and philosopher. Created analytic geometry. Destroyed scholasticism and founded modern psychology. Author of the "Cartesian" system. *Cogito, ergo sum* was his foundation stone. From this he derived two other fundamental ideas, the existence of God and the reality of an external world. According to his "corpusecular philosophy," all phenomena of matter depend on the movement of ultimate particles. Beginning with 1629 he lived 20 years in retirement outside of France working on his system. Died in Stockholm. For portraits see Garrison, p. 247, Abry, p. 130 and Pop. Sci. Monthly, Oct., 1890.

**Desmazières, Jean Baptiste Henri Joseph** (1786–1862). French botanist and microscopist, especially noted for his "Plantes cryptogames de France" (1825–1859). Desmazières acquired a fortune in business, which he used for the study of science. For portrait see "Bull. de la Soc. Mycologique de France." Tome XX. Paris, 1904.

**Dessaignes, Victor** (1800–1885). French chemist in Vendôme. Corresponding member of the Academy of Sciences in chemistry.

**Deville** (See Sainte-Claire-Deville).

**Döbereiner, Johann Wolfgang** (1780–1849). German chemist. Professor in Jena. Friend of Goethe.

**Dreyfus, Alfred** (1859 – —). French Captain of Artillery. A Jew. Falsely accused by military men and anti-Semites of selling or giving military secrets to Germany. Arrested (1894), condemned, degraded (1895), and sent for life to Devil's Island in the Atlantic near French Guiana. The effort on the part of the French liberals to free him and convict the really guilty parties, who were other military officers (Major Esterhazy and Colonel Henry), nearly disrupted the French Government, but was finally successful, and Col. Henry committed suicide. Zola defended Dreyfus in "L'affaire

Dreyfus." With the exception of the noble and brave Col. Picquart, the French war department chiefs, almost to a man, insisted on his guilt, even after his innocence was established, and they were ably supported in their iniquity by the clergy, religious orders, and all anti-Jewish influences. The authorities refused to reopen the case; Col. Picquart was ordered to Tunis and subsequently imprisoned; Esterhazy, who had been accused by Dreyfus, was tried by court martial behind closed doors and acquitted; Zola was prosecuted and convicted, and fled from Paris; and Dreyfus, finally retried by court martial at Rennes, was again convicted but with "extenuating circumstances;" Maître Labori, his leading attorney, was shot during the trial; the President of France was insulted; and Paul Déroulède, the poet, urged the military to destroy the republic. The injustice of the judgment at Rennes was so apparent and so flagrant that Dreyfus was pardoned (1899), but all France was in a ferment which did not subside for several years. Dreyfus demanded another trial which was finally granted in 1905 and this time he was fully acquitted. Dreyfus and Picquart were then restored to the army with promotions and when Clemenceau selected his first cabinet he made General Picquart minister of war. The disestablishment of the French church and the abolition of the religious orders, as dangerous to the republic, was a direct consequence of the Dreyfus affair.

**Du Bois-Reymond, Émile** (1818–1896). German physiologist and philosopher, of Swiss-French extraction. Author of many books. "Ignorabimus" is his famous word. Born and died in Berlin. His brother Paul was a mathematician. For portraits see Garrison, p. 564, Pagel, p. 210, and Pop. Sci. Monthly, July, 1878.

**Duboué,** (—— ———). French physician. Early student of rabies.

**Duclaux, Émile** (1840–1904). French chemist, bacteriologist, pathologist and rural economist. Director of the Pasteur Institute from 1895–1904, and closely associated with it from its beginning in 1888. For a bibliography of Duclaux's writings (220 titles including 9 books, two of which are on milk) see the appendix to Dr. Roux's Review of Duclaux's work in "Ann. de l'Inst. Pasteur," No. 6, 1904, pp. 354–362.

"Les amis qui ont été le plus mêlés à son existence n'ont jamais surpris en lui la moindre défaillance morale; il reste pour eux le modèle auquel ils voudraient ressembler." (Dr. Roux.)

**Duclaux, Madame Mary** (1857 ———). English literary woman, née Agnes Mary Robinson, wife of James Darmesteter, the French orientalist, then of Émile Duclaux (1901). Poet and prose writer in English and French. Author of many books.

- Duclaux, Pierre Justin** (1798–1860). Father of Émile Duclaux.
- Dujardin, Félix** (1801–1860). French zoologist, student of Vermees, Rhizopods, etc. He left unfinished a "Natural History of Echinodermes."
- Dumas, Jean Baptiste André** (1800–1884). French chemist. Member of the Academy of Sciences. Professor in the Sorbonne, Minister of Agriculture and Commerce. Senator. Succeeded Guizot in the Académie Française and was followed by Renan. Determined the atomic weight of many elements. Studied amyl alcohol; discovered the law of substitutions, which upset the ideas of Berzelius. Published a great treatise (in 8 volumes) on applied chemistry. For portraits see Harper's Mag., 1898, p. 625, and Pop. Sci. Monthly, 1880, p. 145.
- "I attend at the Sorbonne the lectures of M. Dumas, a celebrated chemist. You cannot imagine what a crowd of people come to these lectures. The room is immense, and always quite full \* \* \* there are always six or seven hundred people." (Pasteur in 1842.)
- "Le premier banc était réservé aux élèves de l'École normale. J'écoutais, j'applaudissais, je sortais de chacune de ces leçons l'esprit tourné vers de vaste projets." (Pasteur in 1895.)
- Dusch, Theodor Freiherr von** (1824 – —). German pathologist. Student of Henle. Professor in Heidelberg. Wrote on Icterus, brain sinus thrombosis, and diseases of the heart. Collaborated with H. Schröder in the discovery of cotton as a dry (air) filter for bacteria ("Ueber Filtration der Luft in Beziehung auf Fäulniss und Gährung." Ann. der Ch. u. Pharm., Bd. 89, p. 232, Heidelberg, 1854). For portrait see Pagel, p. 431.
- Duval, or Duval-Jouve, Joseph** (1810–1883). French botanist. Studied Equisetums and anatomy of grasses. Father of the anatomist. For portrait see Wittrock II, Tafl. 138.
- Ehrenberg, Christian Gottfried** (1795–1876). German medical man, naturalist and traveler. Author of many elaborate and important works on microscopic organisms, partly in Latin, and many of them magnificently illustrated. Ehrenberg discovered fossil infusoria and laid the foundations of our knowledge of this group of animals. Traveled with Humboldt in Asia and with Hemprich in Egypt. Opposed to the theory of spontaneous generation. For portraits see Pop. Sci. Monthly, March, 1879, and Werkmeister, 1901, 5, pl. 481.
- Fabroni, J. Valentin** (1752–1822). Italian chemist and engineer.
- Farges, Agnès** (— — —). Mother of Émile Duclaux.
- "Tous les mendiants de la ville connaissaient le chemin de sa porte."  
(Madame Duclaux.)

- Feltz, Victor Timothée** (1835–1893). French pathologist. Associated with Coze.
- Fernbach, Ernst** (—— ———). French pathologist at the Pasteur Institute.
- Fracastoro, Girolamo** (1483–1553). Italian physician and poet. Famous for his learning. Born in Verona. Wrote in verse “Syphilis, sive morbus Gallicus” (1530). This is said to be the first use of the word syphilis. For portrait see Garrison, p. 219.
- Fraenkel, Albert** (1848 ———). German physician, bacteriologist and pathologist. Discovered the pneumococcus. For portrait see Pagel, p. 535.
- France, Anatole**, pseudonym of Jacques Anatole Thibault (1844 ———). Greatest of living French stylists. Author of many books and papers, the most interesting of which, perhaps, are certain stories about children, and four volumes of literary criticism entitled “La vie littéraire.” A master of irony. It was he who said of Zola’s novel “La Rêve”: “I marvel it can be so heavy, being so flat!” For portraits see “Les Annales,” No. 1729. Aug. 13, 1916.
- Frémy, Edmond** (1814–1894). French chemist. Member of the Academy of Sciences. Wrote with Pelouze a “Traité de chimie générale” (7 vols.). Editor of the “Encyclopédie de Chimie,” (11 vols.).
- Frey, Heinrich** (1822–1890). German anatomist and zoologist. Professor in Zurich. Collaborated with Leuckart. Published a book on the microscope which passed through many editions, and a book on the elements of histology which had several editions.
- Gay-Lussac, Joseph Louis** (1778–1850). French physicist and chemist. Member of the Academy of Sciences. Peer of France. An elevated, simple, disinterested, ingenious and philosophic mind. Discovered the law of expansion of gases known as Gay-Lussac’s law, also various other laws. In 1804 made two balloon ascensions. First prepared with Thénard the alkali metals, sodium and potassium, in quantity from their salts. Also with Thénard showed chlorine to be a simple substance. Developed alkalimetry and acidimetry. A friend and companion of Humboldt, who styled him (1850): “ce grand et beau caractère.” At 16 he was without knowledge of the sciences. He learned mathematics without a teacher and tutored his way through college, studying at night. For portraits see Harper’s Mag., 1897, p. 757, and Werekmeister, 1899, v. 2, pl. 214.
- Gernez, Désiré Jean Baptiste** (1834 ———). French chemist. Student at the Normal School. Assisted Pasteur in the study of wines and of silkworm diseases. Officer of the Legion of Honor. Member of the Academy of Sciences. Professor in the Normal School (1898–1904). Author of “Crystallization of supersaturated solutions,” etc.

- Gibier, Paul** (1851–1900). French pathologist.
- Grancher, Jacques Joseph** (1843–1907). French physician. Professor in the Faculty of Medicine. Member of the Academy of Medicine. Collaborated with Vulpian in vaccinating men for prevention of rabies. Wrote on rabies, tuberculosis and pneumonia. One of the Editors of "Ann. de l'Inst. Pasteur."
- Guérin, Alphonse François Marie** (1817–1895). French surgeon. Member of the Academy of Medicine and Commander of the Legion of Honor. An introducer of antiseptic methods into French surgery (after the war of 1870).
- Guérin, Jules René** (1801–1886). French physician. Editor of the "Gazette médicale de Paris." Founded an orthopædic institute. Opponent of the preceding. Challenged Pasteur to a duel as result of a dispute over vaccines.
- Guérin-Mèneville, Félix Edouard** (1799–1874). French zoologist and entomologist. Born in Toulon, died in Paris. Wrote a "Guide to silkworm culture" (1856).
- Guyon, Casmir Jean Félix** (1831 – —). French physician and surgeon. Following Pasteur, early to apply antiseptics to diseases of the bladder and urethra. Commander of the Legion of Honor, Professor in the Faculty of Medicine. Member of the Academy of Medicine, etc. Author of an atlas of a hundred plates on urinary diseases (1881–1885). For portrait see Pagel, p. 667.
- Hales, Stephen** (1677–1761). English botanist, physicist and inventor. Wrote "Statical Essays" (1727) and "Hæmastatics" (1733). One of the founders of scientific physiology. For portraits see Garrison, p. 317, and Wittrock II, Tafel. 22.
- Hallier, Ernst** (1831–1904). German botanist. Assistant to Schleiden, Professor in Jena. Author of many books. Quarreled with De Bary. Much of his scientific work was vitiated by his ideas on species transmutation. Unable to reason correctly from premises. Wrote on philosophy and æsthetics toward the end of his life.
- Hameau, Jean** (1779–1851). French physician of La Teste, with ideas somewhat like Henle's. Author of "Étude sur les virus." For portrait see "Arch. d. Parasit.," T. 2, p. 317.
- Haüy, René-Just** (1743–1822). French mineralogist. Member of the Institute. Founder of crystallography. His "Essai d'une théorie sur la structure des cristaux" was published in 1784. Brother of Valentine Haüy who invented raised characters for the blind.
- Helmholtz, Hermann Ludwig Ferdinand von** (1821–1894). German physicist, anatomist and physiologist. Published on conservation of energy (1847), optics, electricity and acoustics. Professor in Königsberg, Bonn, Heidelberg, and Berlin. President of the

Pysikalisch-Technischen Reichsanstalt in Berlin. His chief works are on optics and acoustics. Invented the ophthalmoscope (1850). It was he who said: "The only laws I know are the laws of physics." For portraits see Garrison, p. 562, and Pagel, p. 714.

**Helmont, Jean Baptiste van** (1577-1644). Belgian physician and mystic. Invented a system of medicine founded on that of Paracelsus. Discovered the gastric juice, laudanum, carbon dioxide (gas sylvestre) and carbonate of ammonia. Introduced the words "gas" and "ferment" into chemistry. For portrait see Garrison, p. 251.

**Henle, Friederich Gustav Jakob** (1809-1885). German anatomist, physiologist and pathologist. Professor in Zürich, Heidelberg and Göttingen. Published important books and papers on anatomy, physiology, pathology, zoology and anthropology. His paper referred to in the text is his "Pathologischen Untersuchungen" (1840). See also his "Handbuch der rationellen Pathologie" (1853). For portraits see Garrison, p. 473, and Pagel, p. 718.

**Herschel, Sir John Frederick William** (1792-1871). English astronomer. Son of the astronomer Frederick William Herschel. Famous for his catalogues and measurements of double stars. For portraits see "Tennyson and his friends" by Cameron, 1893, pl. 10, and Harper's Mag., 1897, p. 549.

**Hippocrates** (B. C. 460 - —). Greek physician and surgeon. "The father of Medicine." Descended, so said, from Aesculapius. Born in Cos. Pupil of Democritus. A careful observer and great clinician. He emancipated medicine from many superstitions and enjoyed a great reputation as a healer, not only during his life but for centuries after. For portrait from a bust see Garrison, p. 81.

**Hoff** (See Van-t-Hoff).

**Hoffmann, Hermann** (— - —). German mycologist. The person referred to in the text is probably the above, who was professor in Giessen in 1874.

**Hugo, Victor** (1802-1885). French poet. Son of Gen. Hugo. Born at Besançon. Member of the French Academy. Peer of France. Spent 20 years in exile. Great lyric, epic, and dramatic poet. Copious writer of romances and various critical and philosophical essays. Democratic in politics. His published works comprise eighty-two volumes. For portraits and caricatures see Abry, 497, 500, 502, 536, 540, 543.

**Jaillard, Pierre François** (1827-1883). French physician. Professor in Val de Grâce. Associated with Leplat in anthrax studies.

**Jenner, Edward** (1749-1823). English physician. Discovered cowpox vaccine, a preventive of smallpox. His studies of it were begun in 1775 and the first human vaccination was in 1796. His first book,

- with illustrations, "An Inquiry into the Causes and Effects of Cowpox, or Variolæ Vaccinæ," was published in London in 1798. For portraits see Garrison, p. 375, and Pagel, p. 24
- Joly, Nicolas** (1812–1885). French physician and zoologist. Professor of physiology in Toulouse. Member of the Legion of Honor. Wrote on silkworms and their diseases, milk, yeast of beer, man before metals, comparative psychology, German grammar simplified, etc. Antagonist of Pasteur.
- Joubert, Jules François** (1834 – —). French physicist, especially interested in electricity, on which he published two books. Professor at Collège Rollin. One of Pasteur's collaborators. Officer of the Legion of Honor. Ex-president, Soc. de Physique, and of Soc. d'Électriciens.
- Klebs, Edwin** (1834–1913). German physician and pathologist. Virchow's assistant. Assistant or professor in various places: Königsberg, Bern, Würzburg, Prague, Zürich, Asheville, N. C., Chicago (Rush Medical College) and elsewhere. For portrait see Garrison, p. 614.
- Koch, Robert** (1843–1910). German pathologist and bacteriologist. Geheimrat Regierungsrat, Med. rat. Born at Klausthal in the Harz. A great investigator. Studied wound infections and demonstrated their ætiology (1878). Introduced the poured-plate method (1881). Discovered the cause of tuberculosis (1882) and of cholera (1884). For the latter discovery he was given 100,000 marks by the German Government. Introduced tuberculin (1890). In 1891 was made director of the newly founded Institute for Infectious Diseases in Berlin. In 1896 discovered a remedy for rinderpest in South Africa. Studied malaria, sleeping sickness and other diseases in South Africa, which he visited three times. Also studied diseases of men and animals in India. Visited the United States in 1908. For portraits see Garrison, p. 612, Pagel, p. 878, and Pop. Sci. Monthly, Dec., 1889.
- Kützing, Friederich Traugott** (1807–1893). German algologist. Author of "Synopsis Diatomearum" (1833); "Tabulæ phycologicae" (1845–1870, 2 vols., 2,000 colored plates); "Phycologia generalis" (1843); etc. Distributed exiccatti of fresh water algæ (16 parts). For portrait see Wittrock II, Tafel. 64.
- Lackerbauer, P.** (— — —). Painter and photographer who illustrated Pasteur's book on diseases of silkworms.
- Lannelongue, Odilon Marc** (1840–1911). French surgeon and pathologist. Commander of the Legion of Honor. Professor in University of Paris. Senator. Wrote various medical papers, also "Travels Around the World." Friend of Gambetta. His pathological collections are in the Musée Dupuytren. For portrait see Pagel, p. 959.



- Lavoisier, Antoine Laurent** (1743–1794). French chemist and physicist. Member of the Academy of Sciences. One of the greatest investigators of the 18th century. Founder in chief of modern chemistry. He created chemical nomenclature, determined the composition of air and water, determined the rôle of oxygen in respiration and combustion, and showed that the diamond is a form of carbon. "Nothing can be destroyed, nothing can be created" was one of his favorite expressions. He was guillotined during the French Revolution. For portraits see Garrison, p. 325, and Pop. Sci. Monthly, Aug., 1889.
- Le Bel, Joseph Achille** (1847 – —). French chemist. Wrote on stereochemistry.
- Lebert, Hermann** (1813–1878). German physician, pathologist, chemist and microscopist. Author of numerous memoirs in German and French. Studied and collected with Robin in France. Professor in Zürich and Breslau. Wrote on various pathological subjects, including pébrine and cancer.
- Lechartier, Georges Vital** (1837 – —). French chemist. Normalien. Student of Sainte-Claire-Deville. Wrote on the soy bean (Ann. Sci. Agron., Paris, 1903).
- Leeuwenhoek, Antony van** (1632–1723). Dutch microscopist. Sometimes called "The father of microscopy." Was elected member of the Royal Society of London and of the Academy of Sciences of Paris. Discovered infusoria, bacteria, spermatozoa, striped muscle fibers, the capillary circulation and "globules" in the blood. He also discovered spiral vessels and pitted vessels in plants and distinguished between the structure of dicotyledonous and monocotyledonous stems. A man of limited education but great persistency. The first opponent of spontaneous generation. His progenitors were wealthy brewers. For portraits see Garrison, p. 243, and Pop. Sci. Monthly, April, 1901.
- Lefèvre, Amédée** (1798–1869). French physician and chemist.
- Lémery, Louis** (1677–1743) French chemist.
- Lémery, "The Younger"** (— – 1721). French chemist. Brother of above. One of these is probably the person mentioned in the text.
- Leplat, F.** (— – —). French student of anthrax with Jaillaird.
- Liebig, Justus von** (1803–1873). German organic and agricultural chemist. An industrious analyst, a copious writer, and a competent teacher, who attracted students from all parts of Europe. He organized the first chemical laboratory for students. Studied with Thénard and Gay-Lussac in Paris. Professor in Giessen and Munich. Discovered chloroform, chloral, aldehyd, hippuric acid, tyrosin and many other substances. Introduced a meat

extract which bears his name. A friend of Wöhler with whom he edited "Annalen der Chemie und Pharmacie." Nearly all of his ideas on biological problems have now been set aside. For portraits see Garrison, p. 492, and Pop. Sci. Monthly, June, 1873.

"As to the opinion which explains putrefaction of animal substances by the presence of microscopic animalculæ, it may be compared to that of a child who would explain the rapidity of the Rhine by attributing it to the violent movement of the numerous mill-wheels of Mayence." (Liebig, 1845.)

**Linnaeus or Linné, Charles de** (1707–1778). Swedish naturalist. Foreign member of the French Academy of Sciences. Knight of the Polar Star. Author of the Linnean system of botany, founded on the reproductive organs. He introduced the binary system of nomenclature, and described many genera and species. A copious writer and diligent collector of plants from many lands. He wrote among other things: "Flora Suecica," "Hortus Upsaliensis," "Systema Naturæ," "Fundamenta Botanica," "Genera Plantarum," "Bibliotheca Botanica," "Critica Botanica," "Classes Plantarum," "Philosophia Botanica," and "Species Plantarum" (1753). For portraits see Wittrock I, Tafl. 2, 2a, 2b, 2c, 3, 3\*, 3\*\*, Wittrock II, Tafl. 25, Garrison, p. 304, and Pop. Sci. Monthly, Oct., 1899.

**Lister, Joseph** (1827–1912). Distinguished English surgeon. Knighted, and President of the Royal Society. Son of a distinguished father. Professor in Edinburgh and King's College in London. The first to reform surgical operations with reference to bacterial infections. He treated wounds with concentrated phenol and operated under a phenol spray. He banished hospital gangrene and from his work at Glasgow (1860–69) dates the beginning of modern surgery. Previous to his improvements, which were stimulated by Pasteur's discoveries, the healing of wounds by first intention was a rare occurrence and suppuration and septic poisoning raged in the surgical wards of hospitals like the plague. For portraits see Minerva XX, Garrison, p. 622, Pagel, p. 1019, and Pop. Sci. Monthly, March, 1898.

**Löffler, Friedrich August Johannes** (1852–1915). German physician, bacteriologist, sanitarian, and pathologist. Son of Gottfried Friedrich Franz Löffler, a distinguished army physician. Robert Koch's pupil. Professor in Greifswald. Member of the Imperial Board of Health. Discovered with Schütz (1882) the cause of glanders; isolated in 1884 the cause of diphtheria (Klebs had seen it in the diphtheritic membranes in 1883); in 1885 stained the organism causing erysipelas of the pig, and furnished the first full account of it. (It was discovered by Pasteur and Thuillier.) With Frosch discovered the first filterable virus (Foot and Mouth disease).

With Uhlworm and Leuckart founded the "Centralblatt für Bakteriologie und Parasitenkunde" (1887). For portrait see Pagel, p. 1034.

**Loir, Adrien** (— — —). Pasteur's nephew. Assistant at the Pasteur Institute. Director of the Pasteur Institute in Tunis.

**Ludwig, Karl Friederich Wilhelm** (1816–1895). German physiologist of same group as Brücke, Helmholtz and Du Bois-Reymond. Professor in Zürich, Marburg, Vienna and Leipzig. A very genial, upright, lovable man and a great teacher. About 200 physiologists studied in his laboratories. Invented the kymograph. For portraits see Garrison, pp. 589 and 592, and Pagel, p. 1055.

**Metchnikoff, Elie** (1845–1916). Russian zoologist and pathologist. Professor in Odessa. Resident many years in Paris. Member of the French Academy of Medicine and of the Royal Society of London. Became vice-director of the Pasteur Institute. Discovered phagocytosis. Wrote a book on "Immunity," another on "Prolongation of Human Life," and a third on "Old Age." For portraits see Garrison, p. 619, and Critic, 1903, p. 391.

**Mill, James** (1773–1836). English economist. Father of John Stuart Mill.

**Mitscherlich, Eilhard** (1794–1863). German physicist and chemist. Professor in Berlin. Discovered at 25 the law of isomorphism (1819), for which he received a gold medal from the Royal Society of London. Determined dimorphism. Described the paratartrates. Discovered benzol, nitrobenzol, etc. Interested also in geology. For portrait see Werekmeister, 1898, v. 1, pl. 100.

"Un jour, dans la bibliothèque de l'École, je lus une note du célèbre chimiste cristallographe Mitscherlich, relative à deux combinaisons salines: le tartrate et le paratartrate de soude et d'ammoniaque. Après en avoir étudié toutes les propriétés, Mitscherlich concluait ainsi: 'La nature et le nombre des atomes, leur arrangement et leurs distances sont les mêmes. Cependant le tartrate dévie le plan de la lumière polarisée et le paratartrate est indifférent.'"

Cette note restait comme un point d'interrogation obstinément placé devant mon esprit. Comment deux substances pouvaient-elles être aussi semblables sans être tout à fait identiques? Des mois et des mois se passèrent. Je fus reçu agrégé des sciences physiques. Cette note de Mitscherlich me poursuivait toujours. Par une série d'expériences dont il est facile de retrouver les commentaires explicatifs dans les comptes rendus de l'Académie des sciences, j'arrivai à séparer le paratartrate de soude et d'ammoniaque en deux sels de dissymétrie inverse et d'action inverse sur le plan de polarisation de la lumière. Coup sur coup les obscurités de la note de Mitscherlich se dissipèrent; la composition et la nature de l'acide

paratartrique furent expliquées; une grande lueur se projeta sur la constitution intime des corps, puisque les principes essentiels à la vie m'apparaissaient comme devant prendre naissance sous l'influence de forces dissymétriques. Ce premier chapitre de physique et de chimie moléculaires devait me conduire à d'autres chapitres utiles à l'histoire de la science. Quelles joies de travail j'ai ressenties pendant ces premières années de recherches!" (Pasteur in 1895.)

**Moitrel d'Élément** (1678–1730). French physicist. Discovered a means of collecting and studying gases. Lived in great poverty and was considered "mad" by his contemporaries. Died in America.

**Molière** (Stage name of Jean Baptiste Poquelin) (1622–1673). French actor and dramatist. He often satirized medical men: "Ils savent la plupart de fort belles humanités, savent parler en beau latin; savent nommer en grec toutes les maladies, les définir et les diviser; mais pour ce qui est de les guérir, c'est ce qu'ils ne savent point du tout." (Le Malade imaginaire.)

"On me vient chercher de tous les côtés; et, si les choses vont toujours de même, je suis d'avis de m'en tenir toute ma vie à la médecine. Je trouve que c'est le métier le meilleur de tous; car, soit qu'on fasse bien, ou soit qu'on fasse mal, on est toujours payé de même sort. . . . Un cordonnier, en faisant de souliers, ne sauroit gâter un morceau de cuir, qu'il n'en paye les pots cassés; mais ici l'on peut gâter un homme sans qu'il en coûte rien. . . . c'est toujours la faute de celui qui meurt." (Le Médecin malgré lui.)

"Molière is the greatest French poet, he is so sane" (Alfred Tennyson). For portraits see Petit Larousse, p. 1467, Oeuvres complètes de Molière, Lahure, Paris, 1858, p. 8, and Abry, p. 231.

**Montaigne, Michel Eyquem de** (1533–1592). French essayist, philosopher and moralist. Hardheaded, always demanding a reason, saturated with medieval and classical learning which bristles on every page, yet kindly and interesting beyond most ancient writers, he fills a place in literature occupied by no other person. For portraits see Abry, p. 105, and "Essais de Michel Montaigne avec des notes de tous les commentateurs. Edition revue sur les textes originaux." Paris, Firmin Didot Frères, Fils et Cie, Libraires. 1870.

"So long as an unaffected style and an appearance of the utmost simplicity and good nature shall charm, so long as the lovers of desultory and cheerful conversation shall be more numerous than those who prefer a lecture or a sermon, so long as reading is sought by the many as an amusement in idleness, or a resource in pain, so long will Montaigne be among the favorite authors of mankind."—(Hallam.)

- “Il faisait trop d’histoires, parlait trop de soi. . . . le sot projet qu’il a de se peindre.” (Pascal.)
- Müntz, Charles Achille** (1846–1917). French agronomist. Member of the Academy of Sciences, Officer of the Legion of Honor. Director of the Laboratories of the National Agronomic Institute.
- Musset, Charles** (— — —). Student of Joly in Toulouse.
- Nägeli, Karl Wilhelm von** (1817–1891). Brilliant Swiss-German botanist. Born near Zurich. Died in Munich. Studied in Zurich, Genoa, and Berlin. Professor in Freiburg, Zurich and Munich. Systematist of higher plants, morphologist, physiologist, algologist, bacteriologist, student of evolution. His discovery of wild *Hieracium* hybrids and of oligodynamic phenomena (effect of very dilute poisons) in living cells are perhaps his best known work. He had a habit of tasting his bacteriological cultures which enabled him to make many fine discriminations but undoubtedly shortened his life (Oscar Loew). Wrote with Schwendener *Das Mikroskop*, 2 ed. 1877. For a list of his books see Meyer’s “*Grosses Konversations-Lexikon*,” Leipzig, 1909. For a portrait see Wittrock II, Tafl. 75.
- Needham, John Turberville** (1713–1781). English Jesuit, physicist and microscopist. Member of the Royal Society. Founded the Academy of Sciences in Brussels and was its director. Wrote “*Microscopical Discoveries*” (1745) and “*Idée sommaire, ou vue générale du système physique et métaphysique sur la génération*” (1780). Engaged in a dispute with Voltaire on miracles. Wrote a book to show that the Chinese written characters indicate descent from the Egyptians. Walter Needham, with whom he is sometimes confused, as in Garrison, p. 318, died before Spallanzani was born.
- Nocard, Edmond Isidore Étienne** (1850–1903). French veterinarian. Professor in Alfort. Member of the Academy of Medicine. Showed in 1880 that the cause of rabies is a non-filterable (solid) virus. He used dog saliva and filtered it through plaster of Paris—what came through was innocuous, what remained on the filter was infectious. Wrote on tuberculosis, glanders, tetanus, rabies, peripneumonia, etc. Author with Leclainche of “*Les maladies microbiennes des Animaux*” (3d edition, 8vo, 2 volumes. Paris, 1905), an important work on parasitic diseases of domestic animals. Was on the Egyptian cholera commission (1883). Nocard was son of a wood merchant. For a portrait see *Rec. de méd. vét.* 8 sér. Tome X, No. 15, 15 août, 1903.
- Noguchi, Hideyo** (1876 — —). Distinguished Japanese pathologist working in the United States. Obtained *Treponema pallidum* in pure culture. Showed connection between syphilis, general paresis and locomotor ataxia by finding the parasite of syphilis

in the brain and cord. Improved syphilitic diagnosis. Cultivated the rabies parasite. Cultivated the yellow fever parasite (*Leptospira icteroides* Nog.) and with it produced the disease in guinea pigs ("Jour. Exp. Med.," vol. 29, No. 6, June 1, 1919).

**Obermeier, Otto Hugo Franz** (1843-1873). German pathologist. Studied the spirillum of recurrent fever in Berlin in 1873. His last paper was "Die crsten Fälle und der Charakter der Berliner Flecktyphusepidemie von 1873 (Berl. klinische Wochenschr., 1873, X, No. 30). Died of cholera while studying an outbreak of this disease. To all such be eternal honor!

**Osimo, Marco** (— - —). Italian student of silkworm diseases. Published in Padua in 1859. Recommended egg-selection as a remedy for pébrine.

**Paracelsus** (1493-1541). German Swiss alchemist and physician. His real name was Theophrastus Bombast von Hohenheim. Paracelsus is said to mean superior to Celsus. Learned, original, obstinate and arrogant, opposed to tradition, a great traveler, a shrewd observer, and a successful healer, he died in poverty, destroyed by fools. He taught the doctrine of signatures and was hostile to Galen. He said: "If nature can instruct irrational animals, can it not much more men?" His works in 10 volumes were published in Basel in 1589-1591. For portraits see Garrison, p. 189, and Pagel, p. 13.

**Pascal, Blaise** (1623-1662). French mathematician, physicist and philosopher. A profound thinker and great prose writer. Invented the omnibus and the calculating machine; made important observations with the barometer in high places. Wrote "Lettres écrites à un Provincial par un de ses amis," a covert arraignment of the Jesuits, in which he is "witty as Molière and eloquent as Bossuet" (Voltaire), and "Pensées sur la religion." A deeply religious Roman Catholic, he abandoned scientific pursuits in 1649 for religious studies and became very ascetic. For portraits see Lettres Provincial, Paris, Firmin Didot Frères, 1846, and, Abry, pp. 200, 208 (masque).

**Pascal, Étienne** (— - —). French advocate. President of the Court of Aids. Father of Blaise Pascal.

**Pasteur, Louis** (1822-1895). French physicist, chemist, microscopist and pathologist. Son of a tanner whose father and grandfather were also tanners. A man with an iron will and a great soul, born for combat and mastery. Professor in Dijon, Strasburg, Lille and Paris. In 1874 the French Government granted him a life annuity of 12,000 francs in consideration of his public services and out of the 556 votes there were only 24 dissenting ones. Nine years later, again through the instrumentality of Paul Bert, this was

increased to 25,000 francs. Pasteur succeeded Littré in the Académie Française. Monuments have been erected to him in Melun, Lille, Arbois, Dôle, Besançon and Paris. Both Roty and Dubois made low relief circular bronze plaques of Pasteur. That by Dubois, especially the larger one (7 inch), is very desirable. There is also a fine bust by Dubois in Copenhagen. For a frank and charming letter at 26, proposing marriage, see "Les Annales," Paris, 2 Février, 1919, p. 105, and [for a vivid description of his personal appearance at the time of his rabies studies, see "Monsieur Taine and Monsieur Pasteur" by Gabriel Hanotaux of the French Academy (*Ibid.*, pp. 102-103). For a bibliography of his principal writings consult "Revue scientifique," 4 sé., tome IV, No. 14, Paris, 1895, pp. 427-431. For portrait as a young man see "Les Annales," l. c., p. 105, and when old, Wittrock II, Tafl. 78.

"At the middle of the last century we did not know much more of the actual causes of the great scourges of the race, the plagues, the fevers and the pestilences, than did the Greeks. Here comes in Pasteur's great work. Before him Egyptian darkness; with his advent a light that brightens more and more as the years give us ever fuller knowledge. \* \* \* It was a study of the processes of fermentation that led Pasteur to the sure ground on which we now stand." (Sir Wm. Osler.)

"Your father is absorbed in his thoughts, talks little, sleeps little, rises at dawn, and, in one word, continues the life I began with him this day thirty-five years ago." (Madame Pasteur, 1884.)

#### Aphorisms and Ideals of Pasteur :

The characteristic of a true theory is its fruitfulness.

Science should not concern itself in any way with the philosophical consequences of its discoveries.

Hypotheses come into our laboratories in armfuls, they fill our registers with projected experiments, they stimulate us to research—and that is all.

The recompense and the ambition of a scientist is to conquer the approbation of his peers and of the masters whom he venerates.

It would seem to me that I was committing a theft if I were to let one day go by without doing some work.

If that teaching [the higher education] is but for a small number, it is with this small number, this élite, that the prosperity, glory and supremacy of a nation rest.

Whatever career you may embrace, look up to an exalted goal; worship great men and great things. [To the students at Edinburgh.

Great is the joy of a teacher whose pupils become masters.

A man of science should think of what will be said of him in the following century, not of the insults or the compliments of one day.

Il y a dans la jeunesse de tout homme de science et sans doute de tout homme de lettres, un jour inoubliable où il a connu, à plein esprit et à plein cœur, des émotions si généreuses, où il s'est senti vivre avec un tel mélange de fierté et de reconnaissance, que le reste de son existence en est éclairé à jamais. Ce jour-là, c'est le jour où il s'approche des maîtres, à qui il doit ses premiers enthousiasmes, dont le nom n'a cessé de lui apparaître dans un rayonnement de gloire. Voir enfin ces allumeurs d'âmes, les entendre, leur parler, leur vouer de près, à côté d'eux, le culte secret que nous leur avons si longtemps gardé dans le silence de notre jeunesse obscure, nous dire leur disciple et ne pas nous sentir trop indignes de l'être! Ah! quel est donc le moment, quelle que soit la fortune de notre carrière, qui vaille ce moment-là et qui nous laisse des émotions aussi profondes?

- Péligot, Eugène Melchoir** (1811–1890). French chemist. A student of silkworms. Pasteur's associate. Wrote "Traité de chimie analytique appliquée à l'agriculture" (1883).
- Perdrix, Charles** (— — —). French pathologist. Normal school assistant.
- Pfeffer, Wilhelm** (1845 — —). German plant physiologist. Professor in University of Leipzig. Author of many papers. Discovered osmotic pressure in plant cells, chemotaxis of bacteria, etc. His extensive and important "Physiology of Plants" has been translated into English by A. J. Ewart (Oxford: Clarendon Press). For portrait see Wittrock II, Tafl. 94, and Pop. Sci. Monthly, Jan., 1897.
- Pfeiffer, August** (1848 — —). German physician, bacteriologist and pathologist. This man, or the next, must be the one named in the text.
- Pfeiffer, Richard** (1858 — —). German physician, sanitarian and bacteriologist. Robt. Koch's assistant. Professor in Breslau. Discoverer of the influenza bacillus. Associated with Carl Fränkel. Wrote on immunity. For portrait see Wittrock II, Tafl. 130.
- Philippi.** The person referred to in the text under this name is Filippo de Filippi (1814–1867) commonly known as *de* Philippi, a distinguished naturalist of Turin and Milan. At one time he was Professor of Zoology in the University of Turin. Afterwards he was Senator. He wrote: *Alcune Osservazioni Anatomico-Fisiologiche sugl'-Insetti in Generale, ed in Particolare sul Bombice del Gelso.*" (Annali della Accad. R. d' Agire. di Turino, Vol. V., 1851, pp. 1–25, 3 plates.)
- Piria, Raffaele** (1815–1865). Italian chemist and patriot (Garabaldian); senator. Wrote "Elements of Inorganic Chemistry;" "Lessons on Fermentation;" "Elements of Organic Chemistry" (2d ed., Turin, 1870), etc.



- Pollender** (— — —). German veterinarian. His paper on the microscopic and microchemical investigation of anthrax blood was published in 1855 in *Vierteljahrschr. f. ger. Med.*, Bd. 8.
- Pouchet, Félix Archimede** (1800–1872). French naturalist. Director of the Museum of Natural History in Rouen. Opponent of Pasteur. His “*Hétérogénie, ou Traité de la génération spontanée, etc.*” was published in Paris in 1859 (pp. 32, 672) and his “*L’Origine de la Vie*” (3d ed.) in Paris in 1868. The Maladetta on which Pouchet opened flasks of hay-infusion, all of which clouded, is a glaciated mountain in the Alps.
- Provostaye, or Hervé de la Provostaye, Frederick** (1812–1863). French crystallographer.
- Quatrefages de Bréau, Jean Louis Armand de** (1810–1892). French anatomist, zoologist and anthropologist. Member of the Royal Society of London. A clear, forcible, fluent writer. He wrote a “*Histoire générale des races humaines*” (1886–1889), and “*La race prussienne*” (1871) which led to a polemic with Virchow. For portrait see *Pop. Sci. Monthly*, March, 1885.
- Quevenne, Theodore Auguste** (1805–1855).
- Rabenhorst, Ludwig** (1806–1881). German botanist. Author of a cryptogamic Flora of Germany; “*Flora Europæa algarum,*” etc., collected and distributed dried cryptogamic plants. Founded “*Hedwigia.*”
- Raulin, Juies** (— — —). French chemist and physicist. Student at the Normal School. Pasteur’s assistant. Professor in Brest, Caen and Lyons. His famous paper “*Études chimiques sur la végétation*” is in *Ann. des Sci. Nat. Bot.* V sér. Tome XI, Paris, 1869, pp. 93–299.
- Rayer, Roger J.** (— — —). French physician and pathologist. Rayer’s account of the discovery of the rods in anthrax blood is in “*C. R. Soc. biol.*,” 1850, p. 141.
- Recklinghausen, Friedrich Daniel von** (1833–1910). German pathological anatomist. Virchow’s student. Assistant in Berlin. Professor in Königsberg, Würzburg, and Strassburg. Author of important papers on inflammation, the lymphatic system, and multiple fibromas. Discovered the wandering cells of the connective tissue and the ameboid movements of living pus cells. His paper on Erysipelas is in Virchow’s *Archiv*, Bd. 60, 1874. For portrait see Pagel, p. 1351.
- Redi, Francesco** (1626–1698). Italian physician and naturalist. Born in Arezzo, practiced in Florence. Discovered the itch mite. Applied the experimental method in natural science. He was also a poet. For portrait see Garrison, p. 245.

- Reess, Max Ferdinand Friedrich** (1845–1901). German mycologist. Professor in Erlangen and director of the botanic garden. Produced the first lichen synthesis. Published "Rust fungi of German Conifers" (1869); "Alcoholic fermentation fungi" (1870); "Nature of Lichens" (1879), etc. For portrait see Wittrock II, Tafl. 125.
- Renan, Ernest** (1823–1892). French Semitic scholar. Born in Brittany. Member of the French Academy. Director of the College of France. One of the most engaging and delightful writers of modern France. Author of "Histoire des origines du Christianisme" (8 vols.); "Histoire du peuple d'Israel" (5 vols.), "Ma Soeur Henriette," "Souvenirs d'enfance et de jeunesse," and many other books. For portraits see Pop. Sci. Monthly, April, 1893, "Souvenirs d'enfance etc." (Nelson ed.) and Abry, p. 630.
- Rindfleisch, Georg Eduard** (1836–1908). German pathological anatomist. Assistant to Heidenhain. Professor in Zürich, Bonn and Würzburg. Author of a handbook of pathological anatomy which passed through many editions. For portrait see Pagel, p. 1391.
- Rossignol, H.** (— — —). French veterinary surgeon of Melun. It was he who collected by subscription money for the famous anthrax experiments at Pouilly-le-Fort.
- Roux, Pierre Paul Émile** (1853 — —). French physician, bacteriologist and pathologist. Pupil of Duclaux. Normal School assistant. Collaborated with Pasteur, Chamberland, etc. Present director of the Pasteur Institute. Dr. Roux has made important contributions on rabies, diphtheria, tetanus and other diseases. His studies of diphtheria with Yersin preceded and laid the foundation for those of Behring and Kitasato. Diphtheritic antitoxin (serum) obtained from vaccinated horses was used by Roux in 1894 in a Paris hospital on hundreds of children with marvellous results. For portraits see "Bacteria in Relation to Plant Diseases," vol. I. Frontispiece. Carnegie Institution of Washington, and McClure's Mag., 1893, p. 338.
- Saint-Simon, Louis de Rouvray, duc de** (1675–1755). Brilliant, biting, picturesque French diarist, especially of the Court of Louis XIV. A great painter of manners. His "Memoirs" in 20 volumes is a vast historical storehouse. For portraits see Abry, p. 296, and Saint-Simon "Mémoires sur le Siècle de Louis XIV, et la Régence." Bibliothèque Larousse, Paris, 1911—a good 4 vol. abridgement.
- "Nul écrivain démocratique n'a porté comme lui le fer rouge dans les ulcères de la noblesse." (Larousse: Grand Dict. universel du XIXe Siècle.)

**Sainte-Claire-Deville, Henri Étienne** (1818–1881). French chemist. Brother of the geologist. Both were Students at Collège Rollin. Professor in the Normal School and in the Sorbonne. Member of the Academy of Sciences. Discovered high temperature disassociation. Studied the silicates. Improved methods of working platinum, aluminium, sodium and magnesium. Discovered nitric anhydride (1849). Obtained in masses, melted and pure, the refractory metals, manganese, chromium, nickel and cobalt; with Caron succeeded in producing, artificially, rubies, sapphires, and oriental emeralds. Induced the Metric Commission to use an alloy of platinum-iridium for its standards and during the last ten years of his life was engaged with his illustrious friend Stas of Belgium in preparing sets of these measures, which were not permitted to vary more than one thousandth of a millimeter. Friend of Pasteur. Collaborated with Wohler, Caron, and Debray. For portraits see "Le Centenaire de l'École normale" (1895), p. 407, and Pop. Sci. Monthly, Feb., 1882.

For a splendid appreciation of Sainte-Claire-Deville by Désiré Gernez see "Le Centenaire de l'École normale." Paris, 1895, pp. 407–425.

"Il est impossible de décider lequel des deux fut le plus grand en lui, de l'homme de science ou de l'homme de bien."

"Puisse son exemple développer, chez les jeunes gens qui s'engagent dans la carrière scientifique, le dévouement à la Science, l'une des formes les plus élevées, les moins bruyantes et les plus pures de l'amour de la Patrie!" (Gernez.)

**Sanson**, (— — —). French pathologist.

**Schröder, H.** (— — —). German chemist. Collaborated with Th. von Dusch on fermentation and also published independently. Wrote many papers on "Volumeconstitution fester Körper."

**Schwann, Theodore** (1810–1882). German physieian and naturalist. Professor in Louvain and Liége. Discovered pepsin in gastric juice. Following Robert Brown's discovery of the nucleus in plant cells (1831) and Schleiden's studies, he discovered the nucleus in animal cells, and showed (1839) that animals and plants are composed of the same (cellular) elements ("Mikroskopische Untersuchungen über die Uebereinstimmung in der Structur und dem Wachsthum der Thiere und Pflanzen," Berlin, 1839). Schwann's observations referred to in the text were published in 1837 in Pogg. Ann. der Physik und Chemie, Bd. XLI, p. 184 ("Vorläufige Mittheilung, betreffend Versuche über die Weingährung und Fäulniss").

**Schulze, Franz** (— — —). German chemist in Berlin. His lucid paper "Vorläufige Mittheilung der Resultate einer experimentellen

Beobachtung über Generatio aequivoca," is in Pogg. Annalen der Physik u. Chemie, Bd. 39, Leipzig, 1836, pp. 487-489.

**Schutzembach,** (— — —). German chemist.

**Sédillot, Charles Emmanuel** (1804-1883). French surgeon. Born in Alsace. Served in the war of 1870 as surgeon. Introduced the word *microbe* (C. R. de l'Acad. des Sci., March 11, 1879). The following is one of his aphorisms: "Le succès des opérations dépend de l'habileté du chirurgien. Le revers accusent notre ignorance ou nos fautes, et la perfection est le but de l'art."

**Sévigné, Madame Marquise de, née Marie de Rabutin-Chantal** (1626-1696). Parisian of the time of Louis XIV. Greatest, with perhaps the exception of Voltaire, of all French letter writers. For a portrait see Abry, p. 189.

"Sa correspondance est un tableau fidèle de la société et des moeurs du XVIIe siècle; c'est un journal des faits les plus intéressants des quarante plus belles années du Siècle de Louis XIV. C'est surtout un des monuments de la littérature française."—(Larousse: Grand Dict. universel du XIXe Siècle.)

**Signol, Jean Jules** (1841-1904). French veterinarian. Signol's confusing discovery in relation to anthrax was announced in 1875.

**Spallanzani, Lazzaro** (1729-1799). Italian physiologist, naturalist, abbé, and traveler. Educated at Bologna. Professor of logic, metaphysics and Greek in Reggio; then of natural history, first in University of Modena (1760-1769), afterward in University of Pavia. One of the most perspicacious minds of the 18th century. It is said that we owe to him our first exact notions of circulation of the blood, digestion, respiration and generation in plants and animals. In 1785 he fertilized eggs by means of spermatozoa. For portrait see Iconogr. di uomini sommi nelle scienze e nelle arti italiane. Napoli, Soc. Editrice (1854) pl. 69.

**Stahl, George Ernst** (1660-1734). German chemist and physician. Opposed Hoffmann and developed a doctrine of psychic influence known as *animism*. Professor in Halle. Physician to the King of Prussia. His "Zymotechnica fundamentalis seu fermentationis theoria generalis" was published at Halle in 1697. For portrait see Pagel, p. 18.

**Strauss, Isidor** (1845 - —). French physician and pathologist. Professor of comparative and experimental pathology in Paris. Co-operated with Chamberland in studies on transmission of anthrax, and with Roux, Nocard and Thuillier on cholera in Egypt. Wrote on cholera in Toulon (1884), etc. For portrait see Pagel, p. 1670.

**Susani, Guido** (— — —). Italian silkworm proprietor. Published several papers on silkworms in Milan, 1870-72. Entertained Pasteur.

- Talamon, Charles** (1850 - —). French physician and pathologist. Student of pneumococcus. Discovered it independently of Fränkel.
- Tennyson, Alfred** (1809-1892). English poet. Laureate and knighted baronet. Son of a clergyman, brother of two other poets, Charles and Frederick T. Born at Somersby, in Lincolnshire, educated at Trinity College, Cambridge. Author of charming lyrics, elegies, odes, epical verse, and dramas. The most distinguished and finished English poet of the 19th century and the one who best expressed the prevalent sentiment of scientific and social unrest, with which he mingled a deep religious strain. He lived a very retired life. "Smokes infinite tobacco" (Carlyle). For portraits see Alfred Lord Tennyson, A memoir by his son (the original 2 vol. ed.) and Cameron's "Tennyson and His Friends."
- Thénard, Louis Jacques de** (1777-1857). French chemist. (See Gay-Lussac.) Professor in the College of France and in the Polytechnic School. Discovered cobalt blue (Thénard's blue) and hydrogen peroxide. With Gay-Lussac discovered boron. Discovered an improved way of making white lead. A great and genial teacher. He is said to have had 40,000 students. His "Traité de chimie élémentaire" passed through six editions and was translated into German. Member of the Institute and Peer of France. For portrait see Arnault. Biog. Nouvelle Contemp. 1825, 19, p. 424.
- Thomas, Philippe Étienne** (1843 - —). French veterinarian.
- Thuillier, Louis Ferdinand** (1856-1883). French pathologist. A student, then brilliant associate of Pasteur. Discovered with Pasteur the cause of "rouget" and a vaccine for it. Collaborated on anthrax and on rabies. Died of cholera in Egypt where he had gone to study a violent outbreak of the disease.  
"C'était une nature profondément méditative et silencieuse," (Pasteur).  
For a brief account of Thuillier by Costantin see "Le Centenaire de l'École normale," Paris, 1895, pp. 540-543.  
There is in the Normal School a bust and a portrait of Thuillier and a marble tablet which says: "Thuillier, mort pour la science."
- Thuret, Gustave Adolphe** (1817-1875). Distinguished French algologist. For a biographie notice and a list of his publications by Ed. Bornet see Ann. Sci. Nat. Bot. 6<sup>sc</sup>, Tome II, pp. 308-360. For portrait see Wittrock II, Taf. 76.
- Tiegel, Ernst** (1849 - —). Swiss bacteriologist. Associate of Klebs.
- Toussaint, Jean Joseph Henri** (1847-1900). French veterinarian. Professor in the school at Toulouse. Toussaint's report to the Minister of Agriculture on anthrax is in "Archives Vétérinaires," 1879. See also "C. R. d. s. de l'Acad. des Sei.," 1880, p. 155.

**Trécul, Auguste Adolphe Lucien** (1818–1896). French botanist. Member of the Academy of Sciences and Chevalier of the Legion of Honor. Made botanical collections in the United States and North Mexico. Adversary of Pasteur.

“Heterogenesis is a natural operation by which life, on the point of abandoning an organized body, concentrates its action on some particles of that body and forms thereof beings quite different from that of the substance which has been borrowed” (Trécul, 1867).

**Turpin, Pierre Jean François** (1775–1840). French artist and botanist. Wrote “*Iconographie végétale*” (Paris, 1841). Illustrated Humboldt’s works.

**Tyndall, John** (1820–1893). English physicist. Studied under Bunsen at Marburg. Professor in the Royal Institution in London. Wrote with Huxley, and independently, on glaciers and showed their movement to be due to fracture and refreezing. Studied heat, light, sound and fermentation. Discovered intermittent sterilization. President of the British Association for the Advancement of Science at the Belfast meeting. A friend of Pasteur and opponent of Bastian. A great teacher and popularizer of modern science. For portraits see *Pop. Sci. Monthly*, Nov., 1872, *Harper’s Mag.*, 1888, p. 831, and *Critic*, 1893, p. 382.

**Van’t Hoff, Jacobus Hendrikus** (1852–1911). Dutch chemist and physicist. Professor in Amsterdam and then in Berlin. A great stereo-chemist and one of the founders of physical chemistry. Born in Rotterdam. In 1876 he was docent in physics in the veterinary school in Utrecht, hence one of the German chemists, who was worsted in an argument, called him “horse doctor.” For portraits see “*Chemisch Weekblad*” Amsterdam, Oct. 15, 1910, and *Les prix Nobel en 1901*, p. 76.

**Van Tieghem, Philippe Edouard Léon** (1839–1914). French botanist. Entered the Normal School in 1858. Professor in the Normal School, in the Sorbonne and in the Museum of Natural History. Member of the Academy of Sciences and of the Legion of Honor. Friend of Pasteur. Author of numerous important researches, chiefly anatomical and morphological. The second edition of his important “*Traité de Botanique*” (pp. xxxi, 1855) was published in Paris in 1891. Editor of “*Ann. des Sci. Nat. Bot.*” for thirty-two years. For portrait see *Ann. des Sci. Nat. Bot.*, Tome XIX, No. 1, 1914.

**Varro, or Varrone.** Roman poet and prose writer of the Second Century. Among many other things he wrote “*Rerum rusticarum.*”

**Vergnette-Lamotte, Gérard Alfred Vicomte de** (1806–1886).

- Viala, Eugène** (— — —). Assistant in rabies vaccinations at the Pasteur Institute. A boy educated by Pasteur, who became a devoted and skillful assistant.
- Virchow, Rudolph** (1821–1902). Distinguished German physician, pathologist, sanitarian, anthropologist, and politician (Prussian). Geheimrat, Medicinalrat. Professor in Würzburg and in Berlin. A man of good judgment, broad views and tremendous energy. Founder of a system of cellular pathology, which has had great influence on modern medicine. His book "Cellular Pathology" passed through four editions. A copious writer. Founded with Reinhardt the "Archiv für pathologische Anatomie und Physiologie." Wrote "The Pathology of Tumors" (1863–67) 3 vols. Had much to do with the canalization and sanitation of Berlin. For portraits see Garrison, p. 603, Pagel, p. 1775, and Werckmeister, 1899, 3, pl. 261.
- Vittadini, Carlo** (— — 1865). Italian mycologist (Milan). His method of distinguishing good silkworm eggs from bad was published in Milan in 1859 ("Actes de l'Institut Lombard," Tome I).
- Voigt,** (— — —). French professor in Lyons. Duclaux's friend.
- Vulpian, Edme Félix Alfred** (1826–1887). French physician, pathologist and physiologist. Professor of Pathological Anatomy in Paris. Perpetual Secretary of the Academy of Sciences. Greatly interested in rabies inoculations. For portrait see Pop. Sci. Monthly, Dec., 1888.
- Waldeyer, Heinrich Wilhelm Gottfried** (1836 — —). German anatomist, pathologist, and histologist. Student of Henle. Professor in Strassburg and in University of Berlin. Director of the Anatomical Institute. One of the founders of the "Archiv für mikroskopische Anatomie." Member of various foreign Academies. For portraits see Garrison, p. 548, and Pagel, p. 1806.
- Weigert, Carl** (1845–1904). Celebrated German histologist. Assistant to Waldeyer, to Lebert, and to Cohnheim. Professor in Frankfort-am-Main and in Leipzig. The first to stain bacteria. Wrote "Erste Färbung von Bakterienhaufen" (1871) and "Färbung der Bakterien mit Anilinfarben" (1875). For portrait see Pagel, p. 1826.
- Weiss, Christian Samuel** (1780–1856). German physicist, mineralogist and crystallographer. Professor in Berlin.
- Willis, Thomas** (1621–1675). English anatomist and physiologist of the brain. For portrait see Garrison, p. 253.
- Wöhler, Friedrich** (1800–1882). German physician and chemist. Studied in Stockholm under Berzelius. Professor in Göttingen. Fellow of the Royal Society of London. Collaborated with Liebig. Studied

the cyanides and benzol compounds, isolated aluminium, beryllium and yttrium. Made many contributions to science. Taught many students. For portraits see *Pop. Sci. Monthly*, Aug., 1880, and *Werckmeister*, 1899, vol. 3, pl. 287.

**Yersin, Alexandre** (1863 - —). French physician and pathologist. Collaborator of Roux in the Pasteur Institute. Studied in the French colonies where he discovered the plague bacillus independently of Kitasato.

**Youriévitich, Serge** (— - —). Attaché of the Russian legation in Paris. Eulogist of Duclaux "*Bull. de l'Inst. général psychologique*," 4 année, No. 4, 1904.







En fait de bien à répandre, le devoir  
ne cesse que là où le pouvoir manque  
L. Pasteur

PASTEUR IN HIS OLD AGE  
(From "Le Centenaire de l'École normale." 1895.)

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