

Method for Preventing Rabies after a Bite

[Comptes rendus de l'Académie des sciences, séance du 26 octobre 1885, CI, p. 765-773 et p. 774. - Bulletin de l'Académie de médecine, séance du 27 octobre 1885, 2^e sér., XIV, p. 1431-1439.]

*The original report of Pasteur to the French Academy of Sciences in 1885 on the successful treatment of Joseph Meister and the start of the treatment of Jean-Baptiste Jupille is presented in translation here. This report, startling in its implications for treatment of the feared disease rabies, did as much as anything to insure the immortality of Louis Pasteur in the annals of science and medicine. The translation was prepared by E. T. and D. V. Cohn from the original French paper read by Louis Pasteur. We also call your attention to an earlier translation by D. Berg that appeared in *The Founders of Modern Medicine* by Elie Metchnikoff, Walden Publications, New York, 1939, pps.379-387.*

The treatment of rabies, that I have presented in my name and in that of my collaborators, in some previous reports, assuredly constituted real progress in the study of this disease, progress nonetheless more scientific than practical. Its application revealed some irregularities. Of some 20 dogs so treated, I was unable to render refractory to rabies to more than 15 or 16.

It was advantageous, on the other hand, to end the treatment with a final very virulent inoculation, an inoculation with a control virus, in order to confirm and reinforce the refractory state. In addition, prudence dictated that one keep the dogs under observation for a longer time than the duration of incubation of the disease produced by the direct inoculation of this last virus. Hence it was occasionally necessary to wait three to four months in order to be assured of the refractory state to rabies. Such problems would have substantially limited the application of the method. In substance, the method would lend itself with difficulty to immediate application, a condition demanded nevertheless, by the accidental and unexpected rabid bites.

It became necessary, if possible, to develop a more rapid method and one capable of giving perfect security, I dare say, to the dog. And how, furthermore, before this was achieved, could one dare to permit under any circumstance a trial in man? After many numberless experiments, so to speak, I developed a prophylactic procedure, practicable and rapid, which given numerous and assured successes in the dog, has given me confidence in the generality of the method and its use in all animals and man himself. This method rests essentially on the following facts:

The inoculation in the rabbit, by trepanation, under the dura mater, of spinal cord of a dog suffering from common street rabies, always elicits rabies in these animals after an average incubation period of about fifteen days. If one passes some virus from the first rabbit to a second, from this to a third, and so forth, in the manner of the previous inoculation, there manifests shortly a tendency more and more pronounced in the diminution of the incubation period required for rabies to appear in the successively incubated rabbits.

After twenty to twenty-five passages from rabbit to rabbit, one encounters an incubation period of eight days which is maintained for an additional period of twenty to twenty-five passages. Then one attains an incubation period of seven days, that one discovers with a striking regularity during a new series of passages up to ninety in number. At least this is the number I am at this moment. And it may be that there is a tendency to a length of incubation of a little less than seven days.

This type of experiment, begun in November 1882, and now three years in duration, which has never been interrupted, and which has never had recourse to another virus other than that from

rabbits successively dead of rabies. Consequently, nothing is easier to have continually at one's disposition, during a consider period of time, a rabid virus of perfect purity, always or almost always identical to itself. This then is the practical nub of the method.

The spinal cords of these rabbits are rabid through their length with a constancy in their virulence. If taking the greatest care possible to maintain purity one removes from these cords sections a few centimeters in length, and then suspends them in dry air, virulence slowly disappears until it is finally disappears. The time required for extinction of virulence varies somewhat with the thickness of the cords but above all with the exterior temperature. The lower the temperature, the longer does the virulence last. (Note: If the rabid spinal cord in a humid state is protected from air by carbon dioxide, virulence is conserved more or less for many months without change in its rabid intensity, provided that it is kept from alteration by external microbial agents.) These results represent the scientific center of the method..

Having established these facts, here is the method to render a dog refractory to rabies in a relatively short time. In a series of flasks in which air is maintained in a dry state by means of pieces of potassium hydroxide deposited on the flask bottom, each day one suspends a thickness of fresh rabid spinal tissue taken from a rabbit dead of rabies, rabies developed after seven day of incubation. Each day as well, one inoculates under the skin of a dog one plain Pravaz syringe of sterilized bouillon, in which one has dispersed a small fragment of one of these desiccated spinal pieces, beginning with a piece most distant in time from when it was worked upon, in order to be quite certain that it isn't at all virulent. (*Note of the Translator: A Pravaz syringe consists of a barrel and a metal plunger containing at its base a pair of leather seals. The full syringe can deliver 1 ml of fluid*). Preliminary studies made this clear. On the following days, one performed the same procedure with less old spinal tissue, separated by an interval of two days, until one reaches the last most virulent spinal tissue, that was placed for only a day or two in the flask. In this manner is the dog rendered immune to rabies. One can inject it with rabid virus under the skin or similarly on the brain surface by trepanation without rabies appearing.

By the application of this method, I had made fifty dogs of all ages and breeds refractory to rabies without a single failure, when unexpectedly on the 6th of July last, three persons from Alsace presented themselves at my laboratory: Theodore Vone, grocer from Meissengot, near Schlestadt, bitten on the arm 4 July, by his own dog that had become rabid; Joseph Meister, 9 years old, also bitten on 4 July at 8 in the morning by the same dog. This child knocked to the ground by the dog carried numerous bites on the hand, legs, thighs, some rather deep that made his walking difficult. The principal bites had been cauterized only twelve hours earlier with carbolic acid, 4 July at 8 p.m. By Dr. Weber of the town. The third person who hadn't been bitten was the mother of little Joseph Meister.

At the autopsy of the dog killed by his master, one found the stomach full of grass, of straw and pieces of wood. The dog was truly rabid. Joseph Meister had been lifted up from beneath him covered with slaver and blood. M. Vone had strong contusions on his arms, but he assured me that his shirt hadn't been pierced by the fangs of the dog. As he had nothing to fear, I told him that he might return to Alsace the same day and he did. But I kept little Joseph Meister and his mother with me.

The weekly meeting of the Academy of Sciences took place precisely on July 6. I saw there our colleague M. Dr. Vulpian to whom I told what had happened. M. Vulpian as well as Dr. Grancher, professor at the Faculty of medicine, were good enough to come to see immediately little Joseph Meister and to establish the condition and number of his wounds. There were not less than 14.

The opinion of our wise colleague and of Dr. Grancher was that by the intensity and the number of bites, Joseph Meister was almost inevitably to come down with rabies. I then told Vulpian and Grancher the new data that I had obtained in the study of rabies since the lecture that I had given in Copenhagen, a year earlier. As the death of this child appeared inevitable, I decided, not

without deep and severe unease, as one can well imagine, to try on Joseph Meister the procedure which had consistently worked in dogs.

My fifty dogs, it is true, hadn't been bitten before I determined their refractory state towards rabies, but I knew that this issue could be dispensed with, as I had already obtained a state resistant to rabies in a large number of dogs after a bite. I had provided evidence this year to the members of the Commission on Rabies of this new and important progress.

In consequence, on July 6, at 8 in the evening, sixty hours after the bites of July 4, and in the presence of Drs. Vulpian and Granter, one injected under a fold of skin in the right hypochondrium, one-half Pravaz syringe of spinal cord of a rabbit dead of rabies on June 21 and conserved since then in a flask of dry air, that is to say for 15 days. The following days new inoculations were made always to the hypochondria in accord with the conditions which I give here in the table:

Table I

<u>One-half Pravaz Syringe</u>		
7 July, 6 p.m.	Spinal cord of 23 June	Spinal cord of 14 days
7 July, 9 a.m.	Spinal cord of 25 June	Spinal cord of 12 days
8 July, 9 a.m.	Spinal cord of 27 June	Spinal cord of 11 days
8 July, 6 p.m.	Spinal cord of 29 June	Spinal cord of 9 days
9 July, 11 a.m.	Spinal cord of 1 July	Spinal cord of 8 days
10 July, 11 a.m.	Spinal cord of 3 July	Spinal cord of 7 days
11 July, 11 a.m.	Spinal cord of 5 July	Spinal cord of 6 days
12 July, 11 a.m.	Spinal cord of 7 July	Spinal cord of 5 days
13 July, 11 a.m.	Spinal cord of 9 July	Spinal cord of 4 days
14 July, 11 a.m.	Spinal cord of 11 July	Spinal cord of 3 days
15 July, 11 a.m.	Spinal cord of 13 July	Spinal cord of 2 days
16 July, 11 a.m.	Spinal cord of 15 July	Spinal cord of 1 day

Thus, I carried the number of inoculations to 13 and to 10 the number of days of treatment. I will say later on that a smaller number of inoculations would have been sufficient. But one will understand that in this first trial I had to be especially cautious.

Because of the diverse spinal cords used, two fresh rabbits were inoculated via trephination with these specimens in order to follow their virulence. Observation of the rabbits allowed one to establish that the specimens of 6, 7, 8, 9, and 10 July were not virulent, by their inability to render the rabbits rabid. The spinal cords of 11, 12, 14, 15 and 16 July were completely virulent and the virulent matter was proportionally stronger and stronger. Rabies appeared after seven days of incubation in the rabbits of 15 and 16 July; after eight days in those of the 12th and 14th; after 15 days in those of 11 July.

In the last days, I had thus inoculated Joseph Meister with the most virulent rabid virus, that of the dog made more potent by a great number of rabbit to rabbit passages, a virus that gives rabies to these animals after seven days of incubation, after eight or ten days in dogs. I was warranted in this activity because of what happened to the fifty dogs of which I have spoken. When the state of immunity is attained one may without harm inoculate the most virulent virus an in whatever amount. It always appears that this has not other effect than consolidating the state of refractoriness to rabies.

Joseph Meister has thus escaped, not only from rabies that his bites would have produced, but also from that which I had inoculated him with in order to check his immunity produced by the treatment -- a rabies more virulent than that of ordinary canine rabies. The final most virulent inoculation has again the advantage of reducing the duration of apprehension that one may have following the course of the bites.. If rabies might break out, it will be evident more quickly with a more virulent virus than due to the bites. From the middle of August, I looked forward with confidence to the health of Joseph Meister. As of today, after three months and three weeks elapsed since the accident, his health has left nothing to be desired.

What interpretation should we give to the new procedure that I have made known to prevent rabies after a bite? Today I have no intention of dealing with this question in a complete fashion. I wish to limit myself to a few preliminary details appropriate to understanding the direction of experiments that I am following with the object of establishing the hypotheses on the best of possible interpretations.

In consideration of the methods of progressive attenuation of the fatal virus, and the process by which one can determine it, and keeping in mind, on one side, the influence of air in the attenuation, the first thought that comes to mind to understand the process, is that the period of incubation of the rabid spinal cord in contact with dry air progressively diminishes the intensity of virulence of the cord up to the point of rendering it inactive. One would be led to believe therefore that the prophylactic method employs first a virus without appreciable activity, subsequently a weak one and finally those more and more virulent. I will show subsequently that the facts are not in agreement with this point of view. I will prove that the decreases in incubation period of communicated rabies, day by day in the rabbits on which I have just reported, in order to test their state of virulence, are due to a diminution in quantity of rabid virus contained in the spinal specimens and not an effect of diminution in their virulence.

Can we admit that the inoculation of a virus, always of identical virulence, should be capable of inducing the refractory state to rabies as a consequence of using very small but increasingly large daily amounts? This is one interpretation of facts of the method that I studied from the experimental point of view.

One may give the new procedure another interpretation again, an interpretation certainly strange at first sight, but which merits every consideration, because it is in accord with certain results already known that offers us the phenomenon of life in the case of some lower creatures, and notably in the case of various pathogenic microbes. Many microbes appear to give rise in their cultures to material that have the property to impede their own development. From the year 1880 I had begun studies in order to determine that the microbes of chicken cholera might produce a sort of poison to this microbe. I have not discovered such a material, but I think today that this study should be repeated -- and I will not fail to do what concerns me -- to work in the presence of pure carbon dioxide.

The microbe of swine erysipelas (swine fever) grows in a various culture media, but the amount formed is so slight and so promptly inhibited in its proportion that sometimes the culture can only be detected as faint silk like waves in the interior of the nutritive medium. One could say at once that there is a product formed that inhibits the development of the microbe, whether it is cultivated in contact with air or *in vacuo*. M. Raulin, my former laboratory assistant, today professor in the Faculté de Lyon, established in his remarkable thesis that he defended in Paris, the 22 March 1870, that the growth of *aspergillus niger* produced a substance that partly arrested the development of this mold when the nutrient medium did not contain iron salts. Could it be that the rabies virus is comprised of two distinct substances, side by side, one which is living and capable of multiplying rapidly in the nervous system, and another, not alive, having the faculty, when in suitable amount to inhibit the development of the first? I will examine experimentally, in a coming Communication, with all the attention it deserves, this third interpretation of the prophylactic procedure for rabies.

I don't have to comment in concluding that perhaps the most serious question to resolve at this moment is the allowable interval between the moment of a bite and when one begins treatment. This interval in the case of Joseph Meister was two and a half days. But it should be expected that this could be much longer. Tuesday last, the 20th of October, with the obliging assistance of M.M. Vulpian and Grancher, I had to treat, under exceptionally serious conditions, a young man of fifteen years, bitten fully six days earlier on each of his two hands. I will commit myself to make known to the Academy what happens in this new trial.

The Academy perhaps cannot hear without emotion the account of the courageous act and the great spirit of the young man which I have begun to treat last Tuesday.. This is a villager, of 15 years, his name Jean-Baptiste Jupille, of Villers-Farlay (Jura), who seeing a dog of suspect bearing, of strong stature, threw himself on a group of six of his little friends, all much younger than himself, threw himself, armed only with his whip, in front of the animal. The dog seized Jupille by the left hand. Jupille then threw the dog to the ground, held him beneath him, opened his jaws with his right hand in order to free his left hand, not with receiving many new bites, then with the cord of his whip, he muzzled him and striking him with his shoes, killed him.