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THE SERUM THERAPEUTICS OF TETANUS. TRIAL
OF THE PREVENTIVE TREATMENT.¹

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WE know to-day that the pathogenic microbes act mainly by the substances which they secrete, or of which they provoke the formation in the media of culture, inert or living, where they develop.

These matters, or toxins as they are called, are not all of the same nature ; some of them may be compared to the alkaloids, ptomaines, or leucomaines. The toxins of the septic vibrio (bacillus of malignant œdema), of the bacillus of black-quarter, of the bacillus of glanders, and of the bacillus of tuberculosis are of this kind. One may, without destroying them or sensibly altering them, submit them to a temperature of 110° to 120° C. ; they are not retained by porcelain filters, and it is therefore easy to study them completely isolated from the microbe which has produced them.

There are others of them, on the contrary, that are more closely approached to the diastases, and which are, like these, extremely sensitive to heat ; the toxins of diphtheria and tetanus, for example, do not resist a temperature of 65°, which is absolutely insufficient to kill the microbes which produce these toxins. Happily, they pass almost without change through porcelain filters ; their study is thus relatively easy. These products are extremely dangerous, and are toxic to a degree that exceeds the power of the imagination. Some cultures of diphtheria are capable, after filtration through porcelain, of

¹ Translation of a paper read before the French Academy of Medicine.

killing in less than forty-eight hours a guinea-pig of the weight of 500 grammes with a dose of one-fifteenth of a cubic centimetre. It is possible to obtain tetanus toxins which are fatal to a guinea-pig in a dose of $\frac{1}{500}$ th cc. (Roux and Vaillard); and we have killed strong healthy horses by injecting them with one-tenth of a cc. (two drops) of these same toxins. There is no snake poison whose power approaches that of these microbial poisons.

One succeeds, however, in rendering refractory to these active poisons animals which in the natural state are extremely sensitive to their action; this is effected by inoculating them either with very small doses of pure toxin, or with toxin heated to 65° or 70° , or with toxin modified in its activity by mixing it with a slightly iodised solution (Gram's solution). The injections ought to be frequently repeated at more or less short intervals, at the same time gradually increasing the quantity of the material injected; in operating in this way prudently and patiently there comes a time when the animal of experiment will support without accident considerable doses of the poison. With MM. Roux and Vaillard, we have thus immunised certain horses so firmly that one could, with impunity, inject at one time into the jugular up to 250 and 300 cc. of the tetanus toxin, which would be enough to kill 2500 horses! Another of our horses has received, as a single intravenous injection, up to 600 cc. of extremely active diphtheria toxin.

How does the animal become refractory to the poison? Why does the poison when introduced in such large doses remain inactive?

The most simple hypothesis which presents itself to the mind is the following: There exists in the tissues of the immunised animal a substance which destroys the poison as fast as it penetrates into the organism. This hypothesis has been defended by two pupils of Koch, viz., Behring and Kitasato, as the result of a memorable experiment which served as the basis of serum therapeutics.

If one mixes with the tetanus or diphtheria toxin some serum of animals immunised against tetanus or diphtheria, the mixture of toxin and serum may be injected with impunity, even in considerable doses, to animals which are most sensitive to the poison; the same result follows if one injects at remote parts of the same guinea-pig on the one hand a most certainly fatal dose of toxin, and on the other hand a very small dose of serum; one may also prevent the death of the animal even if the injection of the serum is later by some hours than the injection of the toxin.

This beautiful experiment seems indeed to establish that the serum of animals immunised against the tetanus or diphtheria poison contains a substance (antitoxin) capable of destroying this poison.

Such, however, is not the case. The facts announced by Behring and Kitasato are absolutely correct, and have everywhere been verified; the experiment has always given the same results, but the interpretation which they have given of it is inexact.

Roux has shown in fact that in the mixture of toxin and antitoxic serum the toxin and the serum conserve the properties which are special to each, and the toxin is not destroyed. In the most sensitive animals the mixture does not remain without effect except in the case of fresh subjects, that is to say, animals which have not previously been subjected to the action of any other microbe or

microbian product; if the mixture is injected under the skin of guinea-pigs that have previously been submitted to the action of cultures of the prodigiosus, streptococcus of strangles, cholera vibrio, or bacillus coli, etc., although the guinea-pigs retain all the appearances of health they succumb with the symptoms and lesions of tetanus or diphtheria. If fresh guinea-pigs resist the inoculation of a mixture of toxin and serum, that is not because the toxin is destroyed, but because the serum exercises on their cells a particular stimulation which augments their energy to such a degree that they become capable of resisting the action of the poison.

But in whatever way one interprets them the facts are none the less exact; the serum of animals vaccinated against tetanus and diphtheria is at once preservative and curative, and it may be utilised either as a vaccin or as a therapeutic agent.¹

But it must not be forgotten that although the immunity conferred by the injection of an appropriate dose of serum is acquired immediately, or as soon as the injected liquid has been absorbed, it does not last long; it disappears promptly after four, five, or six weeks, according to the case; in this respect it is very inferior to the immunity which results from vaccination with microbes or with the attenuated toxin. Moreover, the sooner the serum is injected after the inoculation with specific microbes, or after the absorption of the toxin secreted by these microbes, the better does it exert its therapeutic action.

It is this that explains why the serum therapeutics is so efficacious against diphtheria, while it is so feeble against tetanus.

In diphtheria, in fact, one witnesses the evolution of the initial lesion from which the intoxication will proceed; one can therefore intervene before this intoxication has been completely realised, and the sooner one injects the antitoxic serum the more surely will one prevent the effects of the toxin secreted at the seat of the false membrane.

In tetanus, on the contrary, when the first symptoms of the disease are observable, it is already too late to intervene; the first symptoms are the manifestations of the intoxication which has already taken place, and if the quantity of toxin absorbed is sufficient (or the toxin is sufficiently active), nothing will be able to arrest the effects of the intoxication, which has already been silently going on for several days.

Two very simple experiments show that these propositions are well founded. Let us inject under the skin of a fresh guinea-pig one cubic centimetre of this tetanus toxin of which I have just spoken, and which is certainly fatal to guinea-pigs in the dose of $\frac{1}{500}$ th part of a cubic centimetre. If it were a case of a solution of strychnia the animal would be tetanised instantly, but here it is quite different; although the guinea-pig may have received a dose of toxin five hundred times greater than the fatal dose, and although the toxin may have been absorbed in some minutes, nevertheless the animal retains all the appearance of health for twenty, twenty-four, or thirty hours or more. It is only after this long incubation that the first symptoms of tetanus appear. During the whole of this time the

¹ The antitetanic serum may acquire an almost incredible vaccinal power; one of our vaccinated horses furnishes a serum so active that it suffices to inject into a fresh guinea-pig one-trillionth of its weight in order to vaccinate it with certainty against the dose of toxin which is always fatal for guinea-pigs not vaccinated.

toxin absorbed in such large quantity does not remain inactive; it certainly has to exercise on the cells the action which is peculiar to it, and from which the tetanic manifestations proceed. One can therefore easily understand the uselessness of intervention when it is subordinated to the appearance of symptoms showing that the intoxication has already for a long time been realised.

Another experiment shows still better the usually inefficacious results of curative treatment of tetanus, even when one combines with the injection of serum the "eradication of the focus,"—the amputation of the organ bearing the traumatic lesion.

Let us take three long-tailed sheep, and insert in each of them under the skin at the extremity of the tail a small splinter impregnated with dried tetanus spores, and let us then keep these animals carefully under observation, and at the first symptoms of tetanus amputate the tail of each at twenty centimetres above the point of inoculation; finally, let us inject into one of the animals whose tail has been amputated some of the most active antitetanic serum that we have; let us repeat the injections every two hours in the dose of 10, 15, and 20 cc. The three animals will certainly succumb without one being able to note any sensible difference in the evolution of the disease in the test subject, and in those which have been submitted to treatment.¹

It is therefore necessary to renounce for the moment the hope of being able to cure developed cases of tetanus. The treatment by injections of antitetanic serum, which none the less remains rational, has hardly any influence on the disease. The acute cases are almost always certainly fatal; the only cases of tetanus that recover are those which from the outset have a slow progress. Not that all the cases of chronic tetanus by any means recover, but it is only among these that one observes a small number of recoveries.

If one could foresee, as in the case of rabies, what wounds or traumatic injuries have a chance of provoking the disease, nothing would be simpler than to prevent the development of tetanus; it would suffice to inject a little of the antitoxic serum immediately after the production of the wound, and to repeat the injection twice or thrice at an interval of eight days. But we know, alas, that the smallest wound or the most insignificant traumatic injury may provoke tetanus, and one really cannot go to the trouble of submitting to the injections of serum every person who has a wound, a puncture, or an abrasion.

However, there are countries where it appears that umbilical tetanus kills 20, 30, and 40 per cent. of all the new born. Why not there systematically practise an injection of serum to every new-born child on the day of its birth? One would thus save a considerable number of human lives.

In the same way we know that wounds made by the arrows of the natives of the New Hebrides are in most cases followed by tetanus after a short interval. Why not furnish with a supply of antitetanic serum the ships that have to cruise in these latitudes?

Even in France one might diminish the number of cases of tetanus by having recourse more frequently to preventive treatment. If it is

¹ However, it seems that the sheep which has received the serum has less numerous and less intense paroxysms, but all the same it dies as soon as the others.

true that any wound may be followed by tetanus it is equally true that certain wounds are particularly to be feared in this respect.

Gunshot wounds, which are not rare during the shooting season ; wounds produced by crushing, which are so frequent in factories, and wounds soiled by cultivated earth are in this category. The most elementary prudence would suggest that, after having applied the surgical treatment and the dressing appropriate to each of these particular injuries, the surgeon should complete his work by giving the patient an injection of antitetanic serum. At the present time a number of surgeons have adopted this practice.

It is the same in the case of the veterinary surgeon. There are some regions in France where tetanus of the horse is extremely frequent, where it often complicates certain accidental or surgical injuries. Tetanus following castration is far from being rare, and it is one of the accidents which are most prejudicial for the operator. In the north-western suburbs of Paris there exist several Communes where punctures, pricks, gathered nails, quitters, amputations of the tail, wounds of the legs, etc., are commonly followed by tetanus. In all these cases might not one usefully have recourse to preventive injections of anti-toxic serum ?

That is what I have attempted to do ; at the end of last year (December 1894) I intimated to veterinary practitioners that I would send them, on demand, such quantities of antitetanic serum as they might stand in need of.

I have thus distributed during the first six months of 1895 nearly 1800 flasks of 10 cubic centimetres each. I recommended the injection to each subject, under the skin of the neck or behind the shoulder, of 10 cc. of serum, as soon as possible after the infliction of the injury, accidental or operative ; twelve or fifteen days afterwards, one ought to make a second injection of the same dose.

The information which I have been able to obtain regarding the results apply to 375 animals, of which 327 were horses, asses, or mules, 47 lambs, and one ox. Each of these animals received two injections at an interval of fifteen days (20 cc. for the large animals and 10 cc. for the sheep).

The details will be found in the annexed table.

Let me say at once that the serum showed itself in every case absolutely inoffensive, and that not one of the treated animals took tetanus. Without doubt some will consider that 375 cases is too small a number on which to base a conclusion regarding the efficacy of preventive treatment, especially with reference to a disease so rare as tetanus is ; many surgeons and veterinarians have performed a much larger number of operations without having observed a single case of the disease.

The objection is serious, but it will not stand against a minute examination of the annexed table. It will be seen there, for example, that all the animals treated belonged to stables, farms, or hamlets where tetanus had claimed victims some days, weeks, or months previously. A number of them were the actual neighbours of tetanic animals. In some cases the injury was inflicted at the same time and in the same conditions as in other animals which developed tetanus when not treated. Finally, during the six months over which the experiment has extended my twenty-six correspondents, who have not lost a single

RESULTS OF PREVENTIVE INJECTIONS OF ANTITETANIC SERUM.

VETERINARY SURGEONS PRACTISING THE TREATMENT.	ANIMALS TREATED, AND NATURE OF THE INJURY.	REMARKS.
1. Corêt (Aubervilliers).	54 horses : gathered nails and punctures . . . 23 castration 1 docking 2 seton 1 wounds on the legs 27	M. Corêt saw each year from thirty to forty cases of tetanus; this year, during the first six months, he has seen only seven cases of tetanus in horses not submitted to preventive treatment; four had gathered nails or pricks in shoeing; three wounds of the legs.
2. Mollereau (Clarenton).	16 horses : castration and gathered nails.	The majority belonged to two stables in which tetanus had been observed some weeks previously; one was a horse castrated; the other a horse operated on for a complicated sand-crack.
3. Mirot (Cavaillon).	11 horses : 7 castrated. 4 operated on for scirrhous cord.	Observed two cases of tetanus in 1895; one in a mule castrated by an empiric; the other in a mule with a wound of the neck.
4. Chassaing (Pamiers).	3 horses : multiple wounds the result of an accident.	Had two cases of tetanus after castration in horses in 1894.
5. Montsarrat (Mons-en-Puelle).	16 horses : 1 gathered nail. 15 colts castrated.	54 other horses were castrated in 1895 without treatment and without accident.
6. Naudot (Monthard).	8 horses : 4 castrated. 1 operated on for umbilical hernia. 2 docked. 1 gathered nail.	Treated because two other horses wounded in the same accident became tetanic.
7. Mestier (Montargis).	2 horses : 1 wound on the legs. 1 with multiple wounds.	Belonging to a stable where some months previously there had been a case of tetanus in the horse.
8. Caminade (Chazac).	2 horses, castrated.	Belonging to two stables in which tetanus had occurred in 1894.
9. Anvray (Saint-Amand-le-Vendôme).	2 horses : 1 castrated. 1 wound of the coronet.	In a stable in which there had previously been a case of tetanus. Occupying a stall in which, in 1894, a filly had died from tetanus after the same operation.
10. Delmotte (Ferrière-la-Grande).	1 horse, docked.	One of the animals docked was the neighbour to a tetanic horse; the other belonged to a farm where the lambs were decimated by umbilical tetanus.
11. Coutier (Attigny).	4 horses : 3 docked, and 1 docked and castrated.	In 1895 M. Naudot has seen tetanus in two horses and fifteen lambs. Neighbour of an animal seized with tetanus nine days after a gathered nail.
		Neighbour to a case of tetanus following amputation of the tail.
		Belonging to a stable in which a case of tetanus after castration occurred some months previously.
		In the only commune in which M. Anvray had annually seen two or three cases of tetanus; the last case, which occurred some days previously, was consecutive to castration.
		Operated on, on the 12th June, at the same time as 2 other colts which became tetanic on the 22nd and 26th June; received 20 cc. of serum on the 28th June; has not been ill.
		Belonging to a farm on which three fatal cases of tetanus in horses had previously occurred.

12. Mathieu (Attigny).
20 horses, castrated.
13. Guignaut (Yerville).
13 horses, castrated.
14. Biot (Pont-sur-Yonne).
8 horses, castrated.
15. Mulotte (Château-Salins).
1 horse, loss of a large piece of skin.
16. Dupont (Mons).
4 year-old colts, operated on for umbilical hernia.
17. Plessey (Herbault).
5 horses, castrated.
18. Picard (Sourdon).
51 horses : 30 castrated.
24 docked.
7 castrated and docked.
19. Vajou (Milly).
3 horses : 1 operated on for hernia.
1 castrated.
1 severe wound inflicted with a horn.
20. Bouquet (Chablis).
1 horse, severe wound on the hock.
21. Marion (Ravières).
5 horses, castrated.
22. Laperrière (Vervins).
87 horses : 47 castrated.
30 docked.
10 multiple wounds the result of falls.
23. Quentin (Seraucourt).
3 horses, castrated.
24. Philippe & Co. (Rouen).
13 horses : 10 castrated.
1 operation for double scirrhus of l. 2 docked.
25. Dieudonné (Einville).
3 horses, severe wounds soiled with earth and dung.
26. Gellez (Carvin).
38 lambs
9 lambs } castrated.
1 horse
1 ox
- All belonging to stables in which tetanus had previously been observed.
- Did not commence the injections till after a horse had died from tetanus consecutive to castration ; one of the thirteen horses treated had a slight attack of tetanus, but after forty-eight hours of fever and stiffness it made a complete recovery.
- Four or five cases of tetanus observed each year.
- Has not seen any in 1885.
- Treated at the same time a horse suffering from tetanus.
- Had so frequently seen tetanus in horses of this age that he had renounced the operation.
- Just seen one case of tetanus in a horse castrated by an empiric.
- Three cases observed during the preceding year.
- Had two cases of tetanus in 1891, six cases in 1892, four in 1893, and three in 1894 ; had only had recourse to the injection where tetanus had previously occurred.
- Castrated in 1885 sixty-three horses that were not injected ; none of them took tetanus.
- Was kept for six hours at the place where a horse had previously died from tetanus.
- In a stable in which tetanus had previously occurred ; M. Vajou at the same time was treating a tetanic horse.
- M. Bouquet had in three years seen eleven cases of tetanus.
- In communes where he had previously observed tetanus.
- M. Laperrière had annually five or six cases of tetanus ; he had operated where the disease had previously been observed. In 1885 he saw three cases of tetanus in three horses not treated.
- In a commune where in preceding years he had observed three cases of tetanus.
- During the same time lost one horse not treated after castration.
- Had lost one during the previous year.
- Tetanus very frequent in the commune in animals and in man.
- The thirty-eight lambs were part of a lot of forty-nine, of which eleven were dead of tetanus.
- The nine lambs, the horse, and the ox occupied buildings adjoining the infected sheep-house.

To sum up : 375 subjects have been subjected to the preventive treatment with success (327 horses, 1 ox, and 47 sheep). During the same time my correspondents have observed 55 cases of tetanus ; (29 horses and 26 lambs).

case out of 375 animals treated, have observed fifty-five cases of tetanus in animals that were not treated, twenty-nine being in horses and twenty-six in sheep.

I do not wish to weary the Academy with the details of the facts observed; I will only ask permission to cite three of the most interesting facts.

First.—In four years, from 1891 to 1894, M. Picard, of Sourdon, lost fifteen horses from tetanus; the disease showed itself either after castration or after docking. Two of the cases occurred in 1891, six in 1892, four in 1893, and three in 1894.

In 1895, M. Picard did not lose one animal after operation, that being the time during which he had adopted the precaution of submitting to the injections of antitoxic serum all the animals belonging to places where tetanus had shown itself in previous years.

The majority of my correspondents have followed the same plan as M. Picard; they have not had recourse to preventive treatment except where they had previously observed cases of tetanus. However, many of them have had to record several cases of tetanus attacking animals that had not been treated.

Does not this fact give considerable value to the 375 observations which I have been able to collect?

Second.—The second fact is still more convincing.

An old fellow-student of my own, M. Coret, veterinary surgeon at Aubervilliers, saw annually for fifteen years from thirty to forty cases of tetanus. During the first six months of 1895 he has submitted to preventive injections of antitoxic serum fifty-four horses with wounds from gathered nails, pricks in shoeing, or wounds of the legs, etc., all being lesions particularly dangerous with regard to tetanus; not one of these animals has become tetanic. However, during this same six months M. Coret was consulted regarding seven horses attacked with tetanus after analogous injuries but not submitted to preventive injections. During the fifteen years M. Coret saw at least fifteen cases of tetanus among horses in the six months; this year he has seen only seven. The difference appears to be the measure of the benefit which has resulted from the new method; at least eight horses have escaped tetanus, thanks to the preventive injections of antitoxic serum.

Third.—Finally, here is a fact which shows that the injections of antitetanic serum may suddenly arrest the mortality in a flock in which tetanus has appeared under the epidemic form consecutive to castration.

On the 21st May 1895 I received from M. Gellez, veterinary surgeon at Carvin, a telegram asking me to send him serum sufficient for forty-nine lambs that had been recently castrated. Nine of them had already succumbed to tetanus; the first injection of 5 cubic centimetres was made on the 22nd May to the forty surviving lambs; two of them died the same day; the thirty-eight others remained well.

The mortality thus ceased on the day after the injection.

The lambs had been castrated by the shepherd on the 2nd May, by the method of ligaturing the cord.

From all these facts, I believe I am justified in concluding that

although the curative treatment of tetanus has still to be found, one could at least, thanks to the injection of antitoxic serum, in large measure reduce the number of victims of this terrible malady.

NOTES ON THE ADMINISTRATION OF CHLOROFORM AS AN ANÆSTHETIC TO THE DOG AND CAT.

By F. HOBDAV, M.R.C.V.S., Royal Veterinary College, London.

IN a text-book on canine diseases, written as recently as 1893, the following paragraph occurs:—"Dogs are notoriously bad subjects for chloroform, and the pretence of keeping a dog anæsthetised for two hours whilst vivisectional experiments have been performed is nothing more than a pretence. No dogs will survive chloroform for two hours, or for one, and very few will recover from complete anæsthesia so produced for ten minutes."

From enquiries that I have made among professional friends, I am led to believe that the opinion expressed in the foregoing quotation is very commonly held, and that many veterinary surgeons consider that the administration of chloroform alone to dogs is attended with very great risks.

The following statistics will, I think, be of value in showing that chloroform alone can be administered to dogs with perfect safety, and that the risk of accident does not lie in the action of the chloroform so much as in the method of administration.

Of course, I do not mean to say that a mishap will never occur; one has only to watch the medical papers to see that even in human patients deaths under chloroform are by no means rare, but I do think that, if it is administered properly, death should not result unless in cases in which some definite cause is discoverable on *post-mortem* examination.

The cases mentioned below have occurred in the Free Clinique of the College, the anæsthetic, in most instances, being given by students of Class C., to whom (particularly Messrs Engel, Pierce, and Gillam) I am indebted for assistance in recording observations. The chloroform was administered in the form of vapour by means of an inhaler, two patterns being used, viz., Junker's and my own.

Each apparatus is formed with the idea of administering only the vapour of chloroform, thus preventing the rubefacient and after-irritant effects of this anæsthetic when placed in contact with the lips.

Anæsthesia can be produced very slowly and carefully, as the amount of vapour which is allowed to enter can be absolutely controlled, and its admixture with plenty of air ensured, by means of a tap. On the slightest sign of danger the ingress of vapour can be stopped, air allowed, and antidotes applied.

The main point of difference between the two inhalers is that Junker's apparatus *forces* a stream of air through chloroform into a mask which fits over the nose and mouth, whilst my apparatus *sucks* or *pumps* a stream of air and chloroform vapour into the inhaler. I consider that this latter method gives a much greater control over the amount sent into the mask, and thus affords greater