

SOME REMARKS ON A CRITICISM OF QUININE INJECTION AND TETANUS.

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IN the JOURNAL OF THE ROYAL ARMY MEDICAL CORPS for April, 1912, an article by Major F. J. Palmer, R.A.M.C., appeared under the heading "Quinine Injection and Tetanus: A Criticism," in which the author ventured to find fault with some experiments carried out by me with the object of throwing some light on the subject of "The Relation of Tetanus to the Hypodermic or Intramuscular Injection of Quinine."

A detailed account of the experiments which I carried out when investigating this subject, and including those which Major Palmer criticizes, will be found in "No. 43 of the Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India." It is not my intention in this article to enter into a discussion of the many points already clearly dealt with by me in my Scientific Memoir. I shall merely deal with a few of the many errors into which Major Palmer has fallen in his criticism.

In the opening paragraphs of his article Major Palmer makes the following statement: "In consequence of the conclusions formed by Lieutenant-Colonel Semple, the intravenous injection of quinine is recommended instead of the intramuscular, but the objections to the intravenous route are many and serious, and it is doubtful whether it will ever seriously take the place of the intramuscular method as a popular means of exhibition."

With the latter half of this quotation I have no fault to find, but on the contrary I would like to add, that in my opinion, neither the hypodermic nor intravenous methods of giving quinine are ever likely to become popular means of exhibition.

I am not aware that I have ever advocated the intravenous administration of quinine to take the place of the intramuscular, and I do not think any of the experiments carried out by me, or the conclusions drawn from them, would encourage anyone else to do so.

It would appear from various remarks in Major Palmer's article that he has a grievance against a particular circular to which he refers, and that he believes this circular is based on the results of my experiments. I have never seen the circular in question, and I know nothing of its contents, except that I have heard one

or two medical officers in India mention that the intramuscular injection of quinine was prohibited in the Army in India owing to cases of tetanus supervening.

As I have already said in my Scientific Memoir, No. 43, p. 59, and in the *Indian Medical Gazette*, for December, 1911, p. 454, I should certainly not recommend anyone to withhold a hypodermic injection of quinine from any case where it was indicated; but, on the other hand, I should be very sorry to recommend this method of giving quinine as a routine measure in all cases. I should confine myself to the exceptional cases in which quinine by this method is indicated, and these I should safeguard by a dose of tetanus antitoxin, especially in those localities of tropical countries where tetanus frequently occurs.

The next point touched on by Major Palmer, and relevant to the subject which he criticizes, is the following :—

“Semple later states that eleven cases of tetanus following quinine injection were brought to his notice, and mentions that in one case he cultivated the tetanus bacillus from the distilled water in which the quinine had been dissolved. The number of cases in which tetanus has possibly occurred from latent infection can thus be reduced to ten. Ten cases occurring in the whole of India and spread over a series of years !”

It would appear from this quotation that Major Palmer assumes that only ten cases occurred in the whole of India. There may have been 110, or even more for anything I know to the contrary. I have certain knowledge of ten cases, but as I said in my Scientific Memoir, p. 3, many hearsay records might be mentioned in which tetanus is said to have followed the hypodermic administration of quinine, and no doubt many of these are authentic, but in the absence of sufficient authority to vouch for their accuracy, one would not be justified in treating information of this kind with the respect due to established facts.

In some of the French Colonies there have been several cases of tetanus following quinine injections. I do not think medical men are in a hurry to publish cases of tetanus following the hypodermic injection of quinine or any other operations. The fact that it is possible to bring about the death of a patient by using a remedy intended to cure, is quite sufficient to stimulate medical men to leave no stone unturned to avoid calamities of this kind. In the words of the late Professor Maclean, “there is something revolting in a death brought about directly or indirectly by a remedy intended to cure.” These were Maclean’s remarks many

years ago when reflecting on six cases of tetanus in India following quinine injections, the details of which had been brought to his notice.

The other points worthy of notice are those in which Major Palmer criticizes some of the tables of experiments given in my Scientific Memoir, and on reading over his comments I was convinced that he had failed to grasp the meaning of the experiments he attempted to criticize, or even the object for which a particular series was carried out.

TABLE IV.—EXPERIMENTS ON GUINEA-PIGS TO PROVE THE INFLUENCE OF QUININE IN PRODUCING FAVOURABLE CONDITIONS FOR TETANUS INFECTION WHEN QUININE IS COMMENCED ONE DAY BEFORE “WASHED TETANUS SPORES” ARE GIVEN.

Number of experiment	Date of injection of spores	Date of injection of quinine	Amount of quinine injected	Result	Remarks
1	August 27, 1910, right hind leg	August 26 to 28	$\frac{1}{2}$ gr. daily for two days on front of chest	Tetanus, September 3. Died, September 6.	Disease local at first, then became general. Tetanus bacilli grew in anaerobic cultivations made from site of injection of spores, and from site of injection of quinine, but not from the liver, or spleen
2	Ditto	Ditto	Ditto	Tetanus, September 2; remained chronic for five weeks, then recovered	Disease localized to the right leg and right side of body; very severe for a week, when daily improvement set in
3	Ditto	Ditto	Ditto	Remained well	—
4	Ditto	Ditto	Ditto	Ditto	—
5 (Control of spores)	Ditto	Nil	Nil	Ditto	—
6 (Control of culture from which spores were prepared.)	$\frac{1}{2}$ c.c. culture, right hind leg	Nil	Nil	Tetanus, August 28. Died, August 30	Local at outset, then became general

This Table shows 50 per cent of infections when quinine is given one day before spores; the quinine was injected on front of the chest, and spores in the hind leg.

As proof of this statement I shall deal with his remarks on the experiments given in Tables IV, VII, VIII, XII and XV in Chapter V of my Scientific Memoir. Other examples might also be given, including his assumption that weight for weight guinea-pigs and man are equally susceptible to quinine, when it is now

well known that these small animals are far more tolerant of quinine than man. The examples I have chosen will suffice to show that Major Palmer could not have carefully read over my Memoir, and that he failed to grasp the meaning of the experiments therein recorded.

To make matters as clear as possible it is necessary to give each of the above mentioned tables separately, together with Major Palmer's criticisms on them and my remarks, so I shall deal with the subject in the order mentioned.

MAJOR PALMER'S CRITICISM ON TABLE IV.

"A dose of quinine equivalent to 64 gr. in man was given before an injection of spores. This was followed by daily injections of quinine equivalent to 64 gr. Two out of four animals developed tetanus. In this case one of the two control animals also developed tetanus, though no quinine had been given; there were thus 50 per cent of infections in both the experimental and control animals, and the result of this experiment is valueless, except to show that the injection of washed spores is not always the harmless procedure Semple would have us believe, and that, as 50 per cent of this series of animals injected with spores but no quinine developed tetanus, a liberal discount must be made for the effect of quinine in some of the cases in which both quinine and spores had been given."

It would appear from this comment that Major Palmer was under the impression that both control animals received "washed tetanus spores," whereas only one received "washed tetanus spores," and was a control on the spores used in experiments 1, 2, 3 and 4; the other control animal received a sample of the culture from which the spores used in the other experiments in this Table had been prepared, and was a control to prove that this culture was virulent, and being a virulent culture of course the animal was bound to contract tetanus. Neither of the control animals received any quinine, a fact which Major Palmer notes correctly.

These experiments show:—

- (1) That of four guinea-pigs which received hypodermic injections of quinine in front of the chest, and "washed tetanus spores" in the hind leg, two developed tetanus.
- (2) That "washed tetanus spores" alone do not cause tetanus in guinea-pigs.
- (3) That the culture of tetanus from which the "washed spores" were prepared was virulent.

It will be seen that this is a different interpretation to what Major Palmer puts on this series of experiments. To anyone acquainted with the meaning of experiments with tetanus, the facts I have noted become apparent on glancing at the table.

TABLE VII.—THE RESULTS OF THIS SERIES OF EXPERIMENTS ON GUINEA-PIGS ARE GIVEN AS AN ILLUSTRATION OF THE IMPORTANCE OF USING PURE CULTURES ONLY WHEN EXPERIMENTING WITH “WASHED TETANUS SPORES,” AND THE NECESSITY FOR CONTROL EXPERIMENTS. THE CULTURE USED HAD GOT ACCIDENTALLY CONTAMINATED WITH ANOTHER SPORE-FORMING BACILLUS.

Number of experiment	Date of injection of spores	Date of injection of quinine	Quantity of quinine injected	Results	Remarks
1	February 25, 1910	February 23 to 25	$\frac{1}{2}$ gr. daily for two days	Tetanus, February 26. Died February 27	This series proves nothing so far as quinine is concerned, owing to the fact that the two controls contracted tetanus. In all seven experiments there was local swelling at the seat of injection of spores, and bacilli resembling malignant oedema present in stained specimens. Both these and tetanus bacilli were isolated by cultivations from two cases (one control and one experiment)
2	Ditto	Ditto	Ditto	Ditto	—
3	Ditto	Ditto	Ditto	Ditto	—
4	Ditto	Ditto	Ditto	Ditto	—
5 and 6 (Controls to spores)	February 25, 1910	Nil	Nil	Ditto	Both controls contracted tetanus, which rendered the series of experiments useless
7 (Control of culture from which spores were prepared)	$\frac{1}{4}$ c.c. tetanus culture, February 25, 1910.	Nil	Nil	Ditto	Symptoms very acute, and disease proved rapidly fatal

A cultivation made from the spores used for this series after heating for five minutes at a temperature of 75° C. grew a mixture of tetanus and other spore-forming bacilli. The series proves that tetanus spores mixed with other spores produce tetanus.

MAJOR PALMER'S CRITICISMS ON TABLE VII.

“The seventh series of experiments proves nothing that the originator desires, but goes far to vitiate most of his other experiments, as the two controls developed tetanus at the same time.

This, again, shows that the injection of washed spores is not always as harmless as the author would have us believe. In this connexion refer also to Table IV, where half the controls developed tetanus."

In my Scientific Memoir I mentioned that owing to an accidental contamination by another spore-bearing germ of the culture from which the "washed tetanus spores" had been prepared, this series proved nothing as far as quinine was concerned, as the two control animals contracted tetanus at the same time as the four experimental ones. I merely gave the series as an illustration of the necessity of using pure "washed spores," and the importance of never omitting control experiments.

It also served as an example of the fact that "washed tetanus spores" when mixed with a contamination produce tetanus when pure "washed spores" would fail to do so, as proved by the numerous control experiments in my Memoir, in which only pure "washed tetanus spores" prepared from virulent cultures were given, and with the result that the animals invariably remained well.

MAJOR PALMER'S CRITICISMS ON TABLE VIII.

"A tetanus culture and not spores was used upon this occasion. A quarter of a cubic centimetre was given, and, when local tetanus was marked, six of the animals were injected with $\frac{1}{2}$ gr. quinine (equivalent to 64 gr. in man). All died. A control animal to which no quinine had been given also died the same day. In five out of six cases a culture was made from the site of injection, but bacilli were not recovered from the blood. Comment is needless here. One does not give large doses of quinine when tetanus is present. Note also that the control died."

The object of this series of experiments is given in the heading for the Table in which they are recorded, viz., to prove whether hypodermic injections of quinine in cases of tetanus infection produce local conditions suitable for the growth of tetanus bacilli, and the results recorded in the Table clearly prove that this is the case. Of course all the animals in the series died, including the control, as all had been inoculated with a living virulent culture of tetanus.

The important point demonstrated by the result of this series of experiments is the fact that in five out of six cases in which quinine was given hypodermically to animals in the early stage of tetanus, a culture of tetanus was obtained after death from the site of

injection of the quinine, although the quinine had been injected on the front of the chest, and the tetanus infection in the hind leg. Similar results will be found recorded in Tables IX and XII of my Scientific Memoir. In 1904, Vincent, of the Pasteur Institute, Paris, when experimenting with quinine and tetanus infections, also obtained results which favour the view that quinine injections produce foci favourable for the growth of tetanus bacilli, and that infection may be conveyed from the original site of the disease to these foci.

TABLE VIII.—EXPERIMENTS ON GUINEA-PIGS TO PROVE WHETHER HYPODERMIC INJECTIONS OF QUININE IN CASES OF TETANUS INFECTION PRODUCE LOCAL CONDITIONS SUITABLE FOR THE GROWTH OF TETANUS BACILLI.

Number of experiment	Date and seat of injection of tetanus culture	Date and seat of injection of quinine	Result	RESULT OF ANÆROBIC CULTIVATIONS MADE AFTER DEATH FROM		Remarks
				Seat of injection of tetanus culture	Seat of injection of quinine	
1	August 25, 1910, right hind leg	August 27, 1910, $\frac{1}{2}$ gr., chest	Tetanus, August 27. Died, August 29	Growth of tetanus bacilli	Growth of tetanus bacilli	Tetanus local at first; then became severe and general after quinine was given. Infection was conveyed from the hind leg to seat of quinine injection on front of chest
2	Ditto	Ditto	Ditto	Ditto	Ditto	Ditto
3	Ditto	Ditto	Ditto	Ditto	Ditto	Ditto
4	Ditto	Ditto	Ditto	Ditto	Ditto	Ditto
5	Ditto	Ditto	Ditto	Ditto	Ditto	Ditto
6	Ditto	Ditto	Ditto	Ditto	No growth of tetanus bacilli	Symptoms same as experiments Nos. 1 to 5
7 (Control of tetanus culture used)	Ditto	Nil	Ditto	Ditto	—	Tetanus local at outset; then became general

In all these experiments the tetanus bacillus was recovered from the seat of injection of culture (hind leg) and in five out of the six cases in which quinine was given, tetanus bacilli were also isolated from the seat of injection of the quinine (chest). The failure to isolate tetanus bacilli from the seat of quinine injection in No. 6 experiment was very probably due to the fact that a hot glass rod was accidentally used to push down into a broth tube the small piece of subcutaneous tissue used to inseminate it. The tetanus bacilli isolated from the seat of injection of quinine were virulent for guinea-pigs.

In all the animals a culture of tetanus was obtained from the seat of injection of the tetanus culture used.

In my Scientific Memoir, pages 39 and 40, I made the following comments on this series of experiments.

In five out of six experiments, infection was conveyed from the original site of infection in the leg to the site of quinine injection on the front of chest. When these results are interpreted, it means that quinine given hypodermically in the early stages of a tetanus infection starts a fresh focus of infection, and a focus from which tetanus bacilli (which have not been injected into it) can be isolated.

The question arises, how did infection get conveyed from the leg to the chest in these cases? One can only surmise that early in tetanus infection the efficiency of the phagocytes is severely taxed, and that some of them re-enter the circulation carrying tetanus spores, and before they have been able to deal successfully with these spores, they get stranded at the site where quinine has been injected, where they find dead tissue under anærobic conditions, the most suitable conditions for the germination of tetanus spores. A spore-infected phagocyte entering the circulation would not be likely to get stranded in healthy living tissue, and if it did, it would not find conditions suitable for the spores to develop, and its phagocytic action would not be interfered with.

As evidence in favour of this might be adduced the fact that after death in cases of tetanus the bacilli are not found in anærobic cultivations made from the internal organs or heart's blood. If Major Palmer had read my Scientific Memoir carefully, he would have seen that in Tables IX, X, XII and XIV, in addition to other results, ample proof is given, that in cases of tetanus the causal organism is not found in the internal organs and blood after death. An exception would have to be made in regard to an internal organ in the case of "visceral tetanus," for the causal organism would be present in the internal organ where the disease originated.

MAJOR PALMER'S CRITICISMS ON TABLE XII.

"In Table XII three monkeys of weights 12 to 14 lb. were injected at two different sites with 4 grs. of quinine (equivalent to 64 gr. in a man) on three successive days. All developed tetanus, and the bacillus was recovered from the site of injection, but cultures made from the blood proved negative. The site of injection of the spores is not mentioned. This is obviously a matter of

TABLE XII.—EXPERIMENT ON MONKEYS WITH “WASHED TETANUS SPORES” AND QUININE.

Number of experiment	Date and seat of injection of $\frac{1}{2}$ c.c. spores	Date and seat of injection of quinine	Result	RESULT OF ANÆROBIC CULTIVATION MADE FROM				Remarks
				Seat of injection of spores	Seat of injection of quinine	Heart	Spleen	
1	September 2, 1910, right <i>hind leg</i>	September 2, 1910, 3 gr., <i>chest</i> . September 3, 4 gr., <i>chest</i> . September 8, 4 gr., <i>chest</i>	Tetanus, September 19. Died, September 26	Growth of tetanus bacilli	Growth of tetanus bacilli	Nil	Nil	Quinine commenced same day as spores. Lockjaw an early symptom, followed by stiffness of neck and shoulder muscles, and difficulty in swallowing
2	September 2, 1910, right <i>hind leg</i>	September 3, 1910, 4 gr., <i>chest</i> . September 4, 4 gr., <i>chest</i> . September 8, 4 gr., <i>chest</i>	Tetanus, September 17. Died, September 20	Growth of tetanus bacilli	Growth of tetanus bacilli	Nil	Nil	Quinine commenced one day after spores. Lockjaw an early symptom, and soon after tetanus became general and very acute
3	September 3, 1910, right <i>hind leg</i>	September 2, 1910, 3 gr., <i>chest</i> . September 3, 4 gr., <i>chest</i> . September 8, 4 gr., <i>chest</i>	Tetanus, September 15. Died, September 21	Growth of tetanus bacilli	Growth of tetanus bacilli	Nil	Nil	Quinine commenced one day before spores. Lockjaw an early symptom, then slow general tetanus set in, finishing up with emprosthotonos
4 (Control of spores used)	September 2, 1910, right <i>hind leg</i>	..	Remained well	—	—	—	—	—
5 (Control of tetanus culture used to prepare spores)	September 2, 1910, 1 c.c. tetanus culture, right <i>hind leg</i>	..	Tetanus, September 4. Died September 5	Growth of tetanus bacilli	—	Nil	Nil	Lockjaw an early and prominent symptom. Opisthotonos marked before death

In No. 1 experiment, immediately after death, a guinea-pig was injected subcutaneously with 3 c.c. of blood taken from the heart, but the animal did not contract tetanus. An anaerobic cultivation made from $\frac{1}{2}$ c.c. of the heart's blood transferred to a broth tube also gave negative results.

It is evident from the results of the experiments recorded in this Table, that quinine, when given hypodermically to monkeys, produces conditions in which pure “washed tetanus spores” become infective, and capable of producing fatal tetanus. It will be observed that lockjaw was an early and prominent symptom in all four cases, and that opisthotonos was present in one case, and emprosthotonos in another.

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extreme importance, as it makes all the difference whether the spores were injected at the same spot as the quinine or at a distance. Note also that as the blood cultures were negative, there could not have been a large number of spores or bacilli in the blood to be carried into a distant focus, and there find a nidus for development.”

TABLE XV.—EXPERIMENTS PROVING THE PRESENCE OF TETANUS GERMS IN NORMAL HUMAN FÆCES.

Number of experiment	Preparation of material used	Cultivation used	Result	Remarks
1	Emulsion of normal fæces in normal saline solution and heated 5 minutes at 80° C.	Anærobic broth culture	Growth of tetanus bacilli	In the four specimens which contained true tetanus bacilli, there were also other spore-forming bacilli, including the pseudo-tetanus bacilli described by Tavel and Zimmerman, but these were easily distinguished from the true form. Four out of the six negative specimens contained pseudo-tetanus bacilli, and other spore-forming germs; numerous spore-forming bacilli with no resemblance to either the true or pseudo-tetanus bacillus were found in the remaining two specimens. In experiments Nos. 1, 6 and 9 the tetanus bacilli isolated were virulent for guinea pigs in small doses. In experiment No. 2 the tetanus bacilli isolated were non-virulent for guinea pigs in a dose of 1 c.c. of a 14 days' culture.
2	Ditto	Ditto	Ditto	
3	Ditto	Ditto	Negative	
4	Ditto	Ditto	Ditto	
5	Ditto	Ditto	Ditto	
6	Ditto	Ditto	Growth of tetanus bacilli	
7	Ditto	Ditto	Negative	
8	Ditto	Ditto	Ditto	
9	Ditto	Ditto	Growth of tetanus bacilli	
10	Ditto	Ditto	Negative	

The experiments in this Table prove that a large percentage of normal healthy persons harbour virulent tetanus bacilli in their intestinal tracts (4 out of 10, or 40 per cent).

In my descriptions of this series of experiments it is clearly and definitely stated that the spores were injected in the right hind leg, and the quinine on front of the chest; and besides, a reference to the Table will make it plain that the sites of injection of quinine and spores are given under two separate headings. The blood from only one of these experiments (No. 1), was used for No. 3 experiment in Table XIV.

Surely Major Palmer must have only glanced at this Series of experiments, otherwise it is impossible to believe that he could have dropped into such glaring inaccuracies.

MAJOR PALMER'S CRITICISMS ON TABLE XV.

"Cultures made from the faeces of ten guinea-pigs proved positive in four cases. In three of these the bacillus was of a virulent type, and in one non-virulent. This experiment has an important bearing on the next series."

Here again Major Palmer must have only glanced at this series of experiments, for it refers to cultivations made from the intestinal contents of ten healthy human beings (and not from guinea-pigs), in which four out of the ten examined gave a growth of tetanus bacilli. Major Palmer, however, correctly remarks that three of the cultures were virulent, and one was non-virulent.

Other examples might be given, such as the criticism of Table XIV., in which Major Palmer states that "the heart blood of three of the animals mentioned in Series XII. was examined with a negative result." As a matter of fact Table XIV. records experiments with blood taken from the hearts of two guinea-pigs and a monkey, and Table XII. records experiments with tetanus spores and quinine on three monkeys and two control monkeys. It is true that the blood from one of these experimental monkeys was used for one of the experiments in Table XIV.

I might further add to the list of errors into which Major Palmer has fallen in his attempt to criticize my memoir, but the few points I have touched upon will suffice.