QUININE INJECTION AND TETANUS: A CRITICISM.

By Major F. J. PALMER.
Royal Army Medical Corps.

A memoir, No. 43, has recently been published by the Government of India detailing some experiments carried out in Kasauli by Lieutenant-Colonel Sir D. Semple, with a view to determining the relation of tetanus to the hypodermic or intramuscular injection of quinine.

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 for administration 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. A hope is expressed that oral administration properly used will render any other method superfluous, but it is precisely in those cases where the oral route is inadmissible for various reasons, or has been tried and failed, that intramuscular administration finds its greatest field of usefulness.

Last hot weather in the plains it was my experience to see many cases of malarial hæmatemesis and melæna. Such cases are evidence of extremely severe malarial infection, and when admitted to hospital the patient is much collapsed, with extremely rapid pulse and every evidence of overwhelming toxæmia. All these cases were given intramuscular injections of the acid hydrochloride of quinine and all recovered. Again, of what use is the oral method of administration in that large clinical group of cases of malaria in which congestion of the liver and spleen with severe vomiting plays such a prominent part? In some cases the vomiting is most intractable. I have known it last for seventy-two hours and be but little checked by even large doses of morphine given hypodermically during that period.

No one would give an intramuscular injection of quinine lightly, or when oral administration was easy and sufficient; but I have mentioned these facts, which every tropical clinician knows only too well, merely to point out the seriousness of discarding such a valuable therapeutic weapon as intramuscular injection of quinine without the gravest possible reasons.

Granted that a few cases of tetanus have occurred, and these were spread over many years, is that in itself a justification for the prohibition of an old and well-tried procedure, unless it can be proved —and up to the hilt—that the incidence of this disease was not due to faulty methods of administration?

Notions of asepsis vary considerably, and I for one have never given an injection of quinine without preparing the skin of a patient as if he were about to undergo an operation.

Before I came to India I was repeatedly told that operation wounds would not heal properly in the hot weather, no matter what precautions were taken. My answer is that during the past hot weather I have, amongst other operations, opened three knee-joints for the removal of displaced cartilage with a confidence justified by perfect results, and this in the month of June in the plains with a failing monsoon.

I only mention this in order to emphasize the fact that what one man may consider a sufficient degree of cleanliness for intramuscular injection need not necessarily be such; if a higher degree of attention were paid to technique, such accidents (few in number as they really have been) would be probably still fewer or altogether vanish in the future.

The purpose of the present article is to point out that the conditions of some of the experiments were highly artificial, and in no way represent what occurs when an injection of quinine is given in the human subject.

Semple's paper opens with some general considerations to show that quinine injection has often been followed by tetanus. The author notes the effect of heat and cold on the development of the disease. He quotes Fourniers Pescay as stating that men marching under a hot sun developed tetanus next day. This proves nothing and indeed is susceptible of quite another explanation. Semple would seem to infer that the exposure to the hot sun on the previous day weakened resistance, and allowed latent spores to develop. Possibly it did so, but one might as well say that the influence of fatigue in causing the early appearance of fever in the course of an enteric attack is the cause that determines the onset of the attack. The truth, however, is that fatigue has converted what would normally have been the incubation period into a febrile one, but the disease was well on the road nevertheless, and the causative organism had obtained an unyielding hold upon the host. I have seen instances of this over and over again in enteric fever in the field.

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! The remainder of the introductory matter is given over to a consideration of the manner in which the toxin acts.

I shall now summarize shortly the various experiments set forth in the report. In all of these I have taken the amount of quinine given and have worked out the equivalent dose for a man of 10 st. weight. This has been done for the purpose of showing the relatively enormous dose of quinine injected, and the highly artificial character of the experiments, which have no parallel when a dose of 5 gr. (which is generally sufficient) is given in the human subject.

In the first group of experiments, Table I, quinine, in doses equivalent in man to 64 and 127 gr. respectively, was given one day before an injection of washed tetanus spores. One out of four animals given $\frac{1}{2}$ gr. of quinine (equals 64 gr. in man) developed tetanus. Comment: washed tetanus spores are not injected into the human circulation unless the operator uses unsterilized water, nor does one give doses of 64 or 127 gr., but only doses of 5 gr., and some clinicians have found even 3 gr. sufficient.

In Table II, injections of quinine equivalent to a dose of 64 gr. in man, were given daily to guinea-pigs previously injected with a non-virulent strain of washed spores. One out of three animals so treated developed tetanus. The same comment applies to this table as to Table I.

In Table III a more virulent strain of spores was used, and with daily injections of quinine equivalent to 64 gr. all four animals developed tetanus, and in one case bacilli were recovered from the site of injection.

In 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.

In Table V six animals were given quinine equivalent to 64 gr. daily. In two the injection was commenced the day before, in two at the same time, and in two a day after the injection of washed tetanus spores. All these animals developed tetanus. This experiment seems much more conclusive than the previous ones, but again the dose is relatively enormous, and in the hypothetical explanation of tetanus supervening after quinine injection the spores have not been injected a few days previously, but hypothetical months.

In Table VI the effect of the cold chamber was tried on an animal into which washed spores had been injected. In another case ½ gr. of quinine was given as well. The two animals developed tetanus. Again the dose is relatively enormous and the tetanus infection simultaneous with the quinine injection.

The seventh series of experiments proves nothing that the originator desires, but goes far to vitiate most of his other experiments, as 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 connection refer also to Table IV, where half the controls developed tetanus.

Table VIII: A tetanus *culture* and not spores was used upon this occasion. A quarter "c.c." was given, and, when local tetanus was marked, six of the animals were injected with ½ gr. of 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.

Table IX: Practically a repetition of the preceding experiment. A culture was injected, and quinine 1 gr. (equivalent to 127 gr. in man) was injected on the same day. Bacilli were recovered from the injection site, but *not* from the internal organs.

Table X: Quinine, morphine, lactic acid, and saline solution were injected into guinea-pigs. Half an hour later an injection of washed spores was given, with the result that the animals which received quinine and lactic acid developed tetanus, and those

which had received morphine and saline did not. The quinine given was ½ gr. (equivalent to 64 gr. in man). Again the dose is enormous, and, as no proof is given that the organisms developed locally at the site of the inoculation of quinine, the results may conceivably be due to phagocytic paralysis, the result of quinine or acid toxæmia. The experiment, however, is a suggestive one, and I shall return to its fuller consideration later.

Table XI: Semple considered that the effect of quinine might be due to local destruction of tissue at the site of injection providing an anaerobic focus, and possibly in part to phagocytic paralysis. Three animals were injected with ½ gr. of quinine mixed with washed tetanus spores, and all developed the disease. Three in whom morphine was mixed with the spores did not. This experiment is a conclusive one, but again the dose is relatively enormous, and the advocates of intramuscular injection do *not* propose to inject tetanus with their very much smaller doses of quinine, but instead maintain that insufficient asepsis, and the introduction of tetanus spores *locally*, at the site of injection, is the cause of the rare instances of tetanus that have been recorded in this connection.

In Table XII three monkeys of weights 12 and 14 lb. were injected at two different sites with 4 gr. of quinine (equivalent to 64 gr. in man) on three successive days, and also injected with tetanus spores. 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 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 XIII: The right hind leg of animals previously inoculated with spores was cut into, and a piece of subcutaneous tissue and muscle removed from the site of a previous injection. Eight animals were examined and a positive culture was obtained in all. The longest interval after injection was six months. This is obviously a most important experiment. If one may make a comment here it is that in a laboratory where investigations are being frequently carried out on a spore-bearing organism like tetanus, and in such a spot as a guinea-pig's groin, soiled with fæcal matter often con-

taining the same organism, the danger of contamination must be extreme. Why did not Semple here perform the crucial experiment of taking a series of animals in which he had injected spores some some months before, and inject them *in another part of the body* with quinine in something even approaching the quantity in which it is given in the human being? Had tetanus then developed the hypothesis of encysted spores in an old wound area springing into activity under the influence of a quinine injection in another part of the body would have been very hard to discredit.

Table XIV: The heart blood of three of the animals mentioned in Series 12 was examined with a negative result. Evidently very few organisms enter the blood from these old injected areas, and unless organisms are present in the blood in some number it is unlikely that one will be carried to a distant small necrotic area and there develop, producing tetanus.

Table XV: Cultures made from emulsions of the fæces of ten guinea-pigs proved positive in four cases. In three of these the bacillus was of virulent type, in one case non-virulent. This experiment has an important bearing on the next series.

Table XVI: Injections of $\frac{3}{4}$ gr. of quinine, repeated in two days, were given to four guinea-pigs. In one case a virulent culture of tetanus was recovered from the site of injection. The dose here would be equivalent to one of 96 gr. in a man 10 st. in weight. The experiment, however, is a very important one, and obviously requires corroboration. Semple thinks the bacillus came from the intestine, but no attempt was made to prove that this animal's intestine contained tetanus bacilli prior to injection. It may possibly have been introduced locally, and the obviously correct thing to do would be to inject quinine in a series of animals which had been definitely proved to harbour the tetanus bacillus in their intestinal contents.

Table XVII: Four guinea-pigs were given an injection of $\frac{3}{4}$ gr. of quinine in the chest, which was repeated after two days. Cultures from the site of injection were negative, as were also those of the intestinal contents.

Table XVIII: The intestinal contents of ten guinea-pigs were examined. In only one was the result positive, and in this case a virulent culture was isolated. Why did not Semple here endeavour to corroborate his result in Experiment 16 by giving quinine injections to this animal, or why did he not give quinine injections to an animal previously fed with tetanus spores?

In Table XIX two animals were given a dose of antitoxin

followed by an injection of tetanus culture, and next day an injection of ¾ gr. of quinine. Both guinea-pigs remained well, and the antitoxin is thus considered an efficient prophylactic. He recommends 10 to 15 c.c. as efficient for two or three weeks.

The question of a lethal dose of quinine is then considered, and 1 gr. per 150 grm. is mentioned as a large dose; which there is little doubt of, as it is equivalent to a dose of 426 gr. in a man of 10 st. weight! In the guinea-pig 1 gr. per 233 grm. of body weight has been sometimes lethal. In rabbits 6 gr. per kilo of body weight is a certain fatal dose.

Having now finished a recapitulation of this series of experiments, it is very difficult to see upon what grounds the hypothesis of infection, under the influence of quinine injection, from a depot of latent tetanus spores, has been deduced. In the whole series there have been only one or two results which in the least tend to support that view, and in these no attempt has been made to corroborate the result by a further series of experiments. One thing the experiments do show clearly, and that is, that quinine in relatively *enormous* doses predisposes to tetanus infection; but so would possibly many other poisons if given in equally large doses. Quinine is a potent protoplasmic poison; witness its action upon the malarial parasite, and in another direction upon germinal cells. That it may induce paralysis of the phagocytes is quite possible; that it may even produce a minute amount of tissue necrosis at the site of the injection I see no reason to doubt, and indeed regard as proved, but that into this minute area tetanus bacilli from a minute wound inflicted months before, and healed at the time of injection, are likely to be carried is extremely improbable. What is the condition of a healed wound which is presumed to contain encysted spores, and at the same time allows these spores to constantly wander through the circulation for months without detriment, to be eventually carried into the capillary leading to to the minute area of necrosis produced by, let us say, a 5-gr. injection of quinine? Why was no attempt made to corroborate the few inconclusive results which are alone consistent with this view? The doses given to the animals experimented on have no parallel in the human subject, and are relatively enormous. I have calculated their equivalent on the basis of a guinea-pig of maximum, and a man of almost minimum, weight. In many cases the doses must have been much greater than this. One thing indeed the experiments show clearly, and that is, that the tetanus spores or bacilli injected along *with* quinine in the same spot almost certainly

induce tetanus if the dose of quinine is a large one, and possibly if it is a small one. They go very little further than this at present. Many men with a large experience of the intramuscular injection of quinine find it rarely necessary to give more than 5 gr. at a single injection, and I have heard one say that 3 gr. is sufficient. Surely the amount of necrosis produced by these doses would be so minute that the necrosed area would be absorbed before a wandering bacillus could find a nidus there.

Remember also that all cultivations from the blood proved uniformly negative. And it is on account of such so-called proof that the use of this valuable method of medication has been forbidden. Granted even that there were an extremely small chance of developing tetanus, would it not be better to run a one in a thousand chance of dying of tetanus, to a one in four, let us say, of severe malarial melæna? The past malarial season, owing to the unusual climatic conditions, has been an extremely mild one. I hope that before the next one arrives it will be left to the medical officer upon the spot, faced as he may be by the issues of life and death, to do his best for his patient untrammelled by orders possibly based upon faulty premises. Let there be the most scrupulous care in the disinfection of the patient's skin, let the syringe and quinine solution be properly sterilized, and it is the belief of many that we shall have heard the last of the bugbear of quinine and tetanus.

It is only a few years ago since I heard a well-known surgeon maintain that silk should never be used as a suture material in hernia cases as it absorbed germs from the neighbouring bowel. Very few surgeons whose asepsis was beyond reproach would maintain that view now.

I know one officer who, after a plague inoculation, had an area of necrosis at the site of injection, evidenced by intermittent discharge for six months. Every time I perform an operation and ligature a vessel, I leave in a wound a much larger area of tissue bound to undergo necrosis than would be produced by a five-grain injection of quinine, and every time I embed a ligature of iodine or chromic catgut I leave a certain amount of dead organic matter in the wounds. Presumably the soldier is subject to as many cuts and scratches and other minute wounds as any other mortal.

Why do not the tetanus spores emerge from their hiding places and get into these spots so favourable to their development? It is because they have not been introduced *directly* into the wound. Are we going to stop plague and possibly even enteric inoculation,

and all surgical procedures, because a minute area of necrosis may be produced by them. Tetanus has been known to occur in operation wounds sometimes, but on nearly every occasion in which this has taken place the bacillus has been isolated from the suture material.

There is another aspect of the question, and that is a clinical one. We are told to use intravenous injection. An intravenous injection is a much more troublesome thing to give than an intramuscular one, and the temperature of the fluid injected when given without special apparatus must always remain a matter of conjecture.

In a collapsed subject the entering of the lumen of a shrunken vein with a needle is not as easy as one might *a priori* imagine, and it is often necessary to expose the vein by a minute cut in such cases. Again, in a child's arm the vein is not always easy to find. Let me give a personal experience of the occasional impossibility of giving an intravenous injection which may sometimes be experienced. Last September a gharri drove wildly up to the hospital in which I happened to be at the time. In it was a distressed father holding a writhing child in his arms. The little one, a child aged 3, had been unwell that morning, and had fallen down in convulsions. Its temperature was 104° F., and the child certainly looked as if it had not long to live. A certain circular had been issued a week before, and I was not allowed to give what I should have otherwise given at once—an intramuscular injection of quinine. As rapidly as possible a douche can with rubber tube attachment and needle were sterilized, but all this meant time. When all was ready I attempted to plunge the needle directly into the median basilic vein, but owing to the incessant convulsive twitchings of the child, was unable to do so; I then made a small incision exposing the vein, and plunged the needle into the vein, but, owing to the convulsions, no matter how the child was held, the needle point jabbed in and out of the vein piercing the vein wall in various directions, and it was evident that most of the fluid, when running at all, was leaking into the tissues beyond the vein wall to there produce the necrotic area we had just been told of. As well have a necrotic area in muscle as around a vein wall, so 3 gr. of bihydrochloride of quinine was got ready for injection, and, as the child seemed about to cease breathing, the exposed vein wall was incised. Blood immediately spurted up 3 ft. in height, as if an artery had been wounded. It was evident that, even if the injection could have been forced into a vein under such pressure, it would

have never reached the general circulation, but would have been dammed back in the peripheral veins. The child still looked as if about to die, so the 3 gr. of the bihydrochloride was injected into the left arm. Within half an hour the convulsions ceased, and the child made a rapid recovery. In this case intramuscular injection was the only possible procedure, as intravenous injection failed.

This is an extreme case, but has been mentioned to show that an intravenous injection may occasionally be a more difficult matter than one might imagine. This paper is a plea for untrammelled clinical action in cases of extreme gravity, and in those only. It may well conclude with the above narration of a clinical case.