

demonstrated, was not the antitoxin originally injected but was antitoxin manufactured by the patient. This possibility need not, however, be discussed, as the object of the experiments was to obtain evidence as to the necessity of giving repeated doses of serum. The evidence provided by the clinical histories confirms the experimental results. Of the 13 patients, seven received no further serum treatment after the intravenous injection, while the other six were given one or more additional doses of serum by intramuscular or subcutaneous injection. If the histories of the patients in these two groups are compared, no difference in the rapidity of the disappearance of symptoms is apparent.

These 13 cases afford no evidence in favour of frequent injections of serum.

#### THE EMPLOYMENT OF HYPNOTIC AND SEDATIVE DRUGS.

The drugs employed in the treatment of these 25 patients were morphia, potassium or sodium bromide, and chloral hydrate. The extent to which hypnotic drugs were employed varied enormously in the different cases.

One patient appears to have consumed during seven days about 10 drachms of potassium bromide and 10 drachms of chloral hydrate. At the end of this period the patient was in a sleepy and comatose condition and the pulse was small, rapid (130), and irregular. Nevertheless, in spite of the very considerable quantity of drugs which had been given, there was well-marked spasm of the jaw, neck, abdomen, and thigh.

On the other hand, in several cases the number of doses of hypnotics given was very small, and in a few no hypnotics were given at all. The majority of the patients to whom but few doses of hypnotic drugs were given made good recoveries and their general condition was far more satisfactory than that of those who had received frequent doses of drugs.

Tetanus toxin is a very efficient poison to the central nervous system and drugs such as chloral and morphia, which are also essentially poisons to the nervous system, should, in the opinion of the writer, be used with considerable caution.

The use of hypnotic drugs in the treatment of tetanus should probably be restricted to the minimum necessary to relieve violent pain and secure necessary sleep. The amount of hypnotic drugs which is absolutely essential must be ascertained by direct trial for each patient. In those cases in which pain can be moderated and sleep secured by relatively small doses, it is unnecessary and probably injurious to give larger amounts. In tetanus, as in other toxic conditions, the less morphia and chloral are given the better are the patient's chances of recovery.

#### SUMMARY AND CONCLUSIONS.

1. All the 25 patients had had suppurating wounds, but in the majority of cases the wounds were not more serious, and the suppuration had not been more considerable than in the average case sent home to a hospital in England. In 4 cases the wounds were of a comparatively trivial nature. In 9 cases the wounds at the time of the onset of tetanus had completely or almost completely healed. If every wounded soldier, irrespective of the size or condition of the wound, was given a prophylactic injection on his arrival in this country, there would in all probability be a still further reduction in the number and severity of cases of tetanus.

2. Compound fractures are a particular source of danger, and were present in 11 of 25 cases of tetanus.

3. In 3 of the 25 cases the disease ran an extremely short and mild course. These were the only three patients who had received a prophylactic injection after their arrival in England.

4. One result of prophylactic injection is to prolong enormously the incubation period, with the result that tetanus may occur after the wounds have completely healed, and the patient has been transferred to a convalescent hospital. Under these circumstances the earliest signs are readily overlooked.

5. The pain associated with the early and local symptoms may lead to a diagnosis of rheumatism or muscular rheumatism.

6. The earliest signs may consist of clonic or tonic contraction of muscles in the immediate neighbourhood of a wound, usually in the nearest flexor group. The signs may remain localised for many days, and it is characteristic of some cases occurring in inoculated patients that the period of onset is enormously prolonged.

7. After a longer or shorter interval generalisation occurs. The muscles of the jaw, neck, and abdomen become stiff.

There is profuse perspiration and the reflexes of the lower limbs are exaggerated. In many cases the pulse-rate may be very rapid and the temperature normal. On the other hand, even in inoculated persons and after a very long incubation period, the disease may begin suddenly with spasm of the muscles of the jaw and neck.

8. Of 5 mild cases treated by intramuscular and subcutaneous injections of serum 5 recovered. Of 14 cases treated chiefly by intravenous injections 13 recovered. Of 5 cases treated by intrathecal with or without other injections 3 recovered. One patient who was given an intravenous and subsequently an intrathecal injection died. If the signs are well localised and are not spreading rapidly intramuscular injections afford an adequate method of treatment. In severe cases, and in those in which signs are generalised, an intravenous injection (30,000 units) under deep chloroform anaesthesia should be given. After such injection the further progress of the disease is usually arrested, and definite improvement may be expected two to seven days later.

9. There is reason to think that the danger of intravenous injection has been exaggerated. The essential principle of serum treatment is to give a very large dose of antitoxin at the earliest possible moment. This object can be most easily attained by the intravenous route.

10. In 4 cases serum treatment was confined to a single intravenous dose of 30,000 units. In 3 other cases no serum was given subsequent to the intravenous injection. In these 7 cases recovery was as rapid as in 6 other cases in which subsequent injections were given. The serum of patients was shown to contain free antitoxin at various intervals up to 39 days after an intravenous injection of 30,000 units.

In conclusion, I desire to express my thanks to Captain Telford who has kindly given me permission to include one of his cases in this series. To Dr. MacConkey, who supplied the tetanus toxin which was used in the experimental portion of the work, my best thanks are due. I also wish to express my thanks to Major Turner, Captain Morley, Captain Walker, and other medical officers in charge of military and auxiliary hospitals who have helped me by supplying material and information which have been of the greatest service in the preparation of this report.

## THE INTRAMUSCULAR VERSUS THE INTRATHECAL ROUTE IN THE TREATMENT OF TETANUS BY THE INJECTION OF ANTITOXIN.

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THE Tetanus Committee has been labouring for a long time trying to impress Army medical officers with the importance of the recognition of the earliest symptoms of tetanus and that time is the all-important element in serum treatment. A delay of an hour may make all the difference between success and failure. It is, therefore, obvious that it is necessary to give antitoxin by the method which enables it to produce its effect with the least delay.

In THE LANCET of Jan. 27th, 1917, a paper appeared, entitled "An Analysis of Recent Cases of Tetanus in the British Expeditionary Force," by Colonel Sir William B. Leishman, A.M.S., and Major A. B. Smallman, R.A.M.C. In this paper it is laid down that the best and most effective route for the injection of antitetanic serum is the intramuscular. As chairman of the Tetanus Committee I have been deputed by the members to question this statement.

In the Memorandum on Tetanus published in November, 1916,<sup>1</sup> the Committee stated that "experimental and clinical evidence has shown that the best results are obtained by intrathecal injections of serum"; and, again, "in a case of tetanus the first thing to do is to give an intrathecal injection of antitoxin." Sir William Leishman and Major Smallman, on the other hand, as the result of the study of their figures, write: "They appear to us to throw very considerable doubt upon the advisability of employing the intrathecal route, either alone or in combination; and, further, they seem to indicate considerable virtues in connexion with the

<sup>1</sup> THE LANCET, Nov. 18th, 1916, p. 873.

employment of the subcutaneous and intramuscular channels, particularly the latter." Also, "We find our suspicions of the thecal and venous routes strengthened, and also some further support for the good impression which has been made on us by a consideration of the results of the subcutaneous and intramuscular routes." In regard to the intrathecal route they consider "that the evidence is pretty strongly against its employment." In conclusion, they place the alternative routes in the following order of merit: intramuscular, subcutaneous, intrathecal, and intravenous.

The difference of opinion on this important point between the Committee and Sir William Leishman and his colleague is therefore plain and manifest. This statement by Sir William Leishman and Major Smallman is even now having a marked effect in the treatment of tetanus in England. Already letters have been received from inspectors of tetanus saying that it will be difficult, if not impossible, in future to get intrathecal injections carried out promptly. It is so much easier to give an intramuscular injection. "Facilis est descensus." Given the choice between the straight and narrow intrathecal route and the broad and easy intramuscular, it is not to be wondered at if the majority choose the latter.

In this paper it is proposed to confine the issue strictly to the thesis, intramuscular *versus* intrathecal injections. It is doubtful if any truth can be arrived at by the study of the figures at our disposal relating to the result of injections of antitoxin in the human subject. There is no uniformity in the treatment of tetanus in man. The men who suffer are also, as a rule, suffering from other grievous maladies—wounds, fractures, septicæmias, pneumonias, heart failure, &c., so that if the man dies it is impossible in many cases properly to assign the cause. But when we take experimental animals to which a constant dose of the poison can be given and in which the effect of the antitoxin can be carefully watched, we are in a much better position to adjudicate on a simple question such as the merits of the two methods of injection. An ounce of experimental fact is worth a ton of speculation. The only argument brought forward, then, will be one based on animal experiment. This, it is hoped, will be considered legitimate, although there is a great difference between tetanus in man and in an experimental monkey. In the former there are living tetanus bacilli, in the latter a weighed quantity of the dead poison. But the question asked in this paper is a restricted one, "Which is the better route—the intrathecal or the intramuscular?" and in trying to arrive at the correct answer an argument taken from animal experiment seems not only to be a fit and proper one, but the only sure one available. The animal used in this experiment is the monkey, and the experimenter is Professor C. S. Sherrington, a member of the Tetanus Committee. The following is a description of the experiment in his own words:—

Some experiments recently conducted at the request of the Committee upon monkeys bear on the relative efficacy of the serum treatment by intramuscular and intrathecal injection respectively. The experiments exhibit the effect of a single injection of antitetanic serum upon a single precurrent dose of tetanus toxin. They show a difference between the results obtained by the intramuscular and intrathecal methods respectively. The contrast seems sufficiently marked to be significant, although the experiments are at present few in number.

For the experiments the same sample of toxin was used throughout. It was kindly provided by Dr. A. T. MacConkey, of the Lister Institute. The minimal lethal dose of it for the monkey was not ascertained; but in eight control experiments carrying the dose down to 0.8 mgm. per kilo. monkey it proved lethal in all, none of the animals surviving the inoculation longer than 5½ days, and all dying of generalised tetanus. These observations have now been carried down to 0.5 mgm., which likewise killed the animal, but less quickly.

The mode of giving the toxin was the same in most of the cases: the weighed dose was inserted as the dried powder into a small cross-cut about 8 mm. long and 4 deep cut in the outer head of the left gastrocnemius muscle; the lips of the muscle wound were then drawn together by a single fine suture and the skin wound closed by stitches. This inoculation and the subsequent injection of antitetanic serum were made under full anaesthesia and with full aseptic precautions. Some of the later experiments have been made with the toxin in solution.

The antitetanic serum used was likewise kindly provided by Dr. MacConkey and its values in U.S.A. units were supplied by him. It was of various degrees of strength in

units per c.cm. In comparative pairs of experiments the sample concentration used was the same.

For the *intramuscular* injections the serum was given in the usual way—under light chloroform anaesthesia; the shaved skin was cleansed and swabbed with iodine; the site chosen was the muscles one-third down the back of the thigh of the limb which had received the toxin. When, as was often the case, the quantity of serum injected was large, part of the dose was given into the muscles at the back of the neck. No local inconvenience resulted to the animal from these injections.

For *intrathecal* injection the animal was anaesthetised, the skin of the top of the back of the neck shaved, cleansed, and swabbed with iodine, and then the atlo-occipital membrane was exposed by suitable incision. Some of the cerebro-spinal fluid was then withdrawn with the syringe needle thrust through the membrane, and without withdrawing the needle the antitetanus serum was then injected. It was usually not possible to introduce more than 3 c.cm. of serum. The needle was then withdrawn and the wound closed with deep and superficial stitches under full asepsis.

A factor of high importance as influencing the success of the serum treatment is length of time elapsing between the giving of the serum and the giving of the toxin; the shorter this interval the more favourable the opportunity for the serum to have effect. This factor and the amount of the dosage of the toxin and serum are exhibited in the accompanying table.

#### TETANUS TOXIN EXPERIMENTS.

##### *Intramuscular and Intrathecal Injections of Antitetanic Serum Compared.*

Monkey's expt. cage number.	Dose of toxin in mgm. per kilo. of monkey.	No. of hours from inoculation of—		Dose of serum in units per kilo. monkey.	Result.
		Toxin to first symptoms	Toxin to giving serum.		
<i>Intramuscular.</i>					
XXXII.	3.5	29	66	2320	Death in 5½ days.
VII.	2.4	30	66	1360	" 6½ "
XXXV.	2.0	30	54	1200	" 10½ "
LXXV.	2.0	30	50	1600	" 7½ "
LXXVII.	2.0	30	74	2100	" 5½ "
XXXIII.	1.8	30	69	1480	" 5½ "
XXIV.	1.7	30	68	2518	" 11½ "
XLI.	1.6	30	50	2083	" 5½ "
IV.	1.6	30	72	850	" 4½ "
XXXVI.	1.5	30	54	1300	" 12½ "
XL.	1.3	30	74	1365	" 5½ "
XXXVII.	1.1	30	93	1250	" 9½ "
<i>Intrathecal.</i>					
XVII.	4.4	28	78	1407	Death in 5½ "
XIX.	4.3	28	78	1956	" 8½ "
XI.	3.5	29	69	1000	Recovery.
XII.	2.7	30	78	910	Recovery.
IX.	2.7	30	69	300	Death in 4½ days.
XX.	2.2	30	71	1478	Recovery.
XXIII.	2.1	30	68	1085	Recovery.
LI.	2.0	28	51	1500	Recovery.
L.	2.0	28	51	1600	Recovery.
XXVI.	2.0	30	54	560	Recovery.
XLVII.	2.0	30	51	1000	Recovery.
LXXVIII.	2.0	30	72	1600	Recovery.
LXV.	2.0	30	78	2250	Death in 5½ days.
LVI.	2.0	34	66	1800	Recovery.
XXVIII.	1.9	30	54	711	Recovery.
III.	1.8	30	72	966	Recovery.
XXXIX.	1.3	30	74	1200	Recovery.
XXIX.	1.1	30	93	571	Death in 11½ days.

It will be seen from the table that the results are distinctly in favour of the efficacy of the intrathecal as against the intramuscular method.

For instance, with a toxin dose of 3.5 mgm. per kilo. animal, serum in a dosage of 2320 units per kilo. animal, given intramuscularly 66 hours after the toxin, hardly appreciably prolonged life; whereas by the intrathecal method the serum in a dosage of 1000 units per kilo. animal, given 69 hours after the toxin, was followed by recovery.

Again, with a toxin dose of 2.4 mgm. per kilo. animal, serum in a dosage of 1360 units per kilo. animal given intramuscularly 66 hours after the toxin, was followed by death from generalised tetanus in 6½ days; whereas with toxin 2.7 mgm. per kilo. animal, serum in a dosage of 910 units per kilo., given intrathecally 78 hours after the toxin, was followed by recovery.

Again, with a toxin dose of 2 mgm. per kilo. animal, serum in a dosage of 1200 units per kilo. animal, given intramuscularly 54 hours after the toxin, was followed by death from generalised tetanus in 10½ days; whereas with the same dose of toxin, serum given intrathecally at the same period after the toxin, in dosage of 560 units, was followed by recovery.

Again, with 1.3 mgm. toxin per kilo. animal, serum in the dosage of 1365 units per kilo., given 74 hours after inoculation intramuscularly did not obviously retard the fatal result. But with the same dosage of toxin, serum given intrathecally

after a similar lapse of time from the toxin inoculation and in somewhat smaller dosage (1200 units per kilo.), was followed by recovery.

Of the group of 12 animals treated intramuscularly none recovered. Of the group of 18 animals treated intrathecally 13 recovered. But the contrast is more marked than that simple comparison might suggest. Reference to the table shows that in the case of one (IX.) of the intrathecal experiments the dose of serum given was much smaller than was tried in any of the intramuscular experiments. In another case (XXIX.) it was less than half the amount given in the experiment (XXXVII.) most comparable with it in the intramuscular group. Further, the doses of toxin given in two other animals which died in the intrathecal group were larger than any of the toxin doses administered under the intramuscular group.

Can any unbiassed person examine Professor Sherrington's results and not be struck at the manifest superiority of the intrathecal over the intramuscular route? In the cases treated intramuscularly the disease was hardly retarded in its fatal result, whereas almost all those treated by the intrathecal route recovered; the few that died had either too much toxin or too little serum given. The proof of the pudding is in the eating of it. Here is no *in vitro* experiment, but definite living animals all stricken by a mortal malady. Treated intramuscularly they all die. Treated intrathecally the great majority live.

## ON THE INTRATHECAL ROUTE FOR THE ADMINISTRATION OF TETANUS ANTITOXIN.

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*With a Note on a Case of Tetanus Successfully Treated. By*  
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THERE are six routes by which tetanus antitoxin may be given in curative treatment. Of these the intracerebral and intraneural routes are unsuited for regular use, and are, by common consent, reserved for special and desperate cases. The other four routes are the subcutaneous, intramuscular, intravenous, and intrathecal; at the present time opinions are still widely divided as to the relative advantages of these. While I am personally an advocate of the intrathecal route, I recognise that there are other observers with an equal right to judge who prefer one or other of the alternative routes. My purpose in this paper is to record my own experience of the intrathecal route, and to set forth, as far as I am able, the reasons which weigh with me in my preference.

It is of interest to analyse the influences which are at work in determining individual judgment on such a matter. The most powerful influence is, I imagine, personal experience; the man who has the misfortune to lose one or two cases early in his trials of a given route naturally conceives a prejudice against it, while with another, who happens to meet with success, the reverse is the case. Failure, no less than success, is apt to occur whatever be the route chosen, and thus chance comes to play some part in one's preference. The military cases of tetanus which are now occurring in this country are not very numerous, for the prophylactic injection of antitoxin has largely controlled the disease, and most of the cases which occur in spite of the injection are greatly modified in their severity, many being cases of local tetanus only. It is probable that a large proportion of these milder cases would recover whatever the route of administration of the serum, or even without serum at all. It thus comes about that the advocate of any route is able to bring forward lists of cases with a large percentage of recoveries, so that it has become more difficult than before to appraise the relative values of the different routes.

### *Conclusions derived from Statistical and Physiological Data.*

A common method by which attempts have been made to reach a decision is the statistical one. If we had sufficiently large series of comparable cases treated each with comparable doses of serum by the four different routes separately it might be easy to draw conclusions from the relative case-mortalities of each series. But such data are not forth-

coming, and we shall probably never get them, for the primary object is always the cure of the patient. As a rule, more than one route is employed in any given case, and the widest discrepancies exist not only as to choice of route but as to dosage of serum, while different cases of tetanus present extreme variations in severity. It does not seem legitimate to draw any conclusions from the heterogeneous mass of data at present available. In his analysis of the cases of tetanus occurring in this country during the first year of the war, Surgeon-General Sir David Bruce found that the mortality was a little lower in those who had received intrathecal injections of serum than in those who had not; but when he came to apply a similar analysis to the cases occurring in the second year of the war this advantage was no longer seen. Last January Colonel Sir W. B. Leishman and Major A. B. Smallman published an elaborate and exhaustive analysis of 160 cases occurring amongst our troops in France during last summer and autumn<sup>1</sup>; their figures brought out the surprising result that the highest mortality was amongst the cases which had received an intravenous injection, while the intrathecal route was not much better; the best apparent results were achieved by the subcutaneous and especially by the intramuscular routes. They state that they are fully aware of the many pitfalls incident to the search for truth amongst small figures dealing with cases presenting many complicating factors, and perhaps the most serious of these are the facts that no less than 61 out of their 113 fatal cases had gas-gangrene, and that cases are included as fatal cases of tetanus whether they died of tetanus or of some complication. Thus of 21 fatal cases treated by intrathecal injection only, 9 were attributed by the reporting officer to causes other than tetanus. There is a natural tendency to employ the more heroic measures of intravenous and intrathecal injection in the more desperate cases and to be content with the simpler procedures in slighter cases; I have certainly been influenced by this tendency myself. Taking into consideration all these sources of fallacy, I cannot but feel that argument from such confused statistical data is a somewhat hazardous proceeding.

There is a third method of justifying a preference for a certain route which is also hazardous. This consists in *a priori* reasoning from supposed physiological data. It is, for example, common to hear it said that the intrathecal route must be the best because thus the antitoxin is brought into the closest relation with the central nervous system; while others, again, defend the intravenous route because the antitoxin is thus carried into the closest attainable contact with the affected motor neurons. The fallacy of such reasoning lies in the fact that it rests on insecure physiological premisses. There is no actual proof that antitoxin can pass from the cerebro-spinal fluid into the substance of the central nervous system, nor any proof that it can reach the neurons from the capillaries adjacent to them. There is no proof that, if these things were true, the antitoxin could dissociate from the neurons the toxin which had already entered into combination with them. Many physiologists hold opinions on these points and arguments can be arrayed on either side, but we have not sufficient proof, or even consensus of opinion, to enable us to reason safely on such a difficult subject as this.

### *The Method of Experiment.*

There remains one method which has been helpful in deciding many vexed questions: it is that of experiment, and I must confess that I place more reliance on this than on any other method in deciding on a choice of route. Though we cannot get "clean data" from human cases of tetanus they can be obtained by animal experiment. It is possible to introduce known and similar doses of tetanus toxin into series of animals, allow the disease to commence, and then determine the route by which equal suitable doses of antitoxin are most successful in saving or prolonging life. More than one series of experiments has been carried out on these lines. In Denmark Permin showed that when tetanus toxin was injected into the muscles in suitable dose local tetanus was prevented when antitoxin was given intrathecally at the same time, whereas it was not prevented by the same dose of antitoxin given intravenously; not even intrathecal injection prevented tetanus if it was given four hours after the toxin. Permin