An Analysis

OF

RECENT CASES OF TETANUS IN THE BRITISH EXPEDITIONARY FORCE,

WITH SPECIAL REFERENCE TO THEIR TREATMENT
BY ANTITOXIN.

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SOME of the medical problems of the war, though of much scientific interest, are less urgent than others, and may well await the leisured study which will without doubt be given to them after its conclusion, but others which are more urgent appear to call for at least a partial attempt to reach agreement before the campaign grows older. Prominent among these appears to us the subject of the specific treatment of tetanus, upon which there exist wide differences of view, both as to the usefulness of antitoxin at all and, admitting its value, as to the system of its employment which may be expected to yield the best results.

Earlier in the war information with regard to tetanus in the Army in France was collected by one of us (W. B. L.) and summarised in one of the sections of the official "Memorandum on the Treatment of Injuries in War," which was published in July, 1915, and circulated to all medical officers. Further experience of the treatment of the disease has accumulated since then, but much of it relates to comparatively small groups of cases observed in a single hospital, and cases fortunately have on the whole been so few that a number of general hospitals may not have seen one for months. Recently a Tetanus Committee appointed by the War Office, under the chairmanship of Surgeon-General Sir David Bruce, has collected a large amount of most useful information in connexion with the cases which have been treated in home hospitals, and have published their results and recommendations, partly in the form of circular memoranda and partly in an article in THE LANCET of Dec. 2nd, 1916, by Sir David Bruce. We have remodelled some of our tables upon those adopted by Sir David Bruce, so that they may be read as complementary one to the other, and may in this way serve to bring into greater relief the points in which the experiences of home hospitals are in contrast or in accord with those acquired in the Expeditionary Force.

Early last summer it was felt that we had reason to anticipate the occurrence of a certain amount of tetanus among the large number of wounded to be expected during the coming offensive on the Somme. Although since the days of the battle of the Aisne strict orders exist that every wounded man should receive a prophylactic injection of tetanus antitoxin, and it is exceedingly rare that this is for any reason omitted, still it is well recognised that this cannot confer absolute protection. The severe character of many of the wounds is only too familiar to us all, and the heavy coating of foul mud, with which skin and uniform are almost always plastered, renders it certain that very large doses of anaerobic and other bacteria are at times driven deeply into the devitalised tissues.

Arrangements were therefore organised for the collection of detailed information in respect of every case of tetanus occurring in France, a number of questions being asked on a form which had to be completed and sent to headquarters on the termination or final disposal of the case. The information given on the sheets was then transferred to cards, which facilitated the analysis of the various points under inquiry. On the whole, the required details have been very accurately recorded, but it will be realised that at times of heavy pressure in field ambulances and casualty clearing stations it is often difficult or impossible to obtain and record the full details on certain points. These must later be ascertained, if at all, from a man who may be too ill to

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cross-examine or who may own the notoriously inaccurate memory of at least the old soldier for such points as dates and hours.

We have classed the cases simply into those who died and those who recovered. At first we divided them into three classes: (1) Those whose deaths were attributed solely to tetanus; (2) those whose deaths were in larger part attributable to complications, such as severe sepsis, gas gangrene, secondary hæmorrhage, &c.; and (3) the recoveries. It was found, however, that the difficulties of deciding in which subdivision to place the fatal cases were too great and too uncertain. A simple distribution into the two classes has the disadvantage that the total deaths from tetanus inevitably include a number of cases in which the condition of the wound, the exhaustion of the patient, or some complication were in themselves quite sufficient to account for death. They also comprise cases in which it was definitely stated that all symptoms of tetanus had disappeared before death. Such cases naturally weigh the scales against whatever system of treatment had been employed for the tetanic symptoms. On the other hand, however, the symptoms recorded in some cases have been so slight as to suggest the possibility that they might not have been due to tetanus at all; and, if this were so, such cases would form a counterweight to those whose death was not due to tetanus.

The present analysis is based upon 160 cases which occurred in hospitals in France between July 1st and Oct. 31st, 1916. Of these cases 118 died and 42 recovered, a case-mortality of 73·7 per cent. This mortality may be contrasted with that of the group of cases, already alluded to, examined by one of us in the spring of 1915. In that series, among 179 cases there were 140 deaths, a case-mortality of 78·2 per cent. This, as far as it goes, does not disclose any considerable degree of improvement in the treatment employed. Both series show a heavier death-rate than that which has been recorded for the cases treated in home hospitals where, during the first year, out of 231 cases analysed by Sir David Bruce, there was a case-mortality of 57·7 per cent. and, for the second year, up to July 31st, 1916, out of 195 cases a mortality of 49·2 per cent.

These four series show a slight improvement in case-mortality on each side of the Channel, but also make it clear that cases are more fatal in France by about 25 per cent. The causes for the latter fact are so obvious as to need no labouring. The most desperate wounds, which it would be dangerous to move, and which are therefore detained in clearing stations or base hospitals, are just those which are most likely to develop tetanus, and, further, the complications of severe sepsis, gas gangrene, &c., which must be more in evidence closer to the line than in home hospitals, more frequently play a large part in determining a fatal issue in cases of tetanus.

INCIDENCE.

It is not permissible at the present moment to give any information upon the actual incidence of the disease among the wounded, or to contrast one period of the war with another from that point of view, but there can be no harm in mentioning an impression, which we have gathered from the figures in question, that the highest incidence will eventually be found to be associated with periods during which heavy fighting took place in wet weather. This, after all, might have been anticipated, as it is obvious that, under such conditions, the change from dust to mud will mean a heavier bacterial inoculation of the wound.

An analysis of the influence of the prophylactic dose of antitoxin upon the general incidence of the disease must, for the same reason, be passed over; but this is, fortunately, a procedure which is so fully accepted, not only by ourselves but by our Allies and our enemies, that it stands in little need of further statistical support. Were it not for the universal acceptance of the protective value of this dose we feel sure that any analysis of the subject would have had to deal not with a few hundred cases but with many thousands.

THE INFLUENCE OF THE SEVERITY AND CONDITION OF THE WOUNDED.

In connexion with each case information was asked for on a number of specific points, and among these were queries as to the existence of severe sepsis or gas-infection of the tissues. Details were also asked to the nature and severity of the wound itself and whether it was single or multiple. Table I. shows the frequency with which these factors were

encountered in each group—i.e., among 113 fatal cases and 42 recovered cases. (It will be understood that, where the total number of cases shown in any table does not reach 160, the required information had not been obtained in every case.)

The table shows, as might be expected, a considerably higher percentage occurrence of these conditions among the fatal cases. The most striking contrast is that shown in the

TABLE I.—*Condition of Wounds as Regards Sepsis, Presence of Gas Gangrene, &c.*

—	Severe sepsis.	Gas gangrene.	Extensive or severe wound.	Multiple wounds.
Fatal—113 cases ...	88 (78%)	61 (54%)	98 (87%)	62 (55%)
Recovered—42 cases ...	24 (57%)	5 (12%)	26 (61%)	18 (43%)

much greater frequency of gas gangrene as a complicating factor in the cases which terminated fatally, no less than 54 per cent. of these cases having been noted as suffering from this grave complication. Its dangerous nature is but too well known, and its frequency among these cases is, to our minds, one of the chief causes of the relatively higher death-rate from tetanus in France as compared with the experience at home.

Another point in connexion with the factors complicating a judgment on the results of treatment appears to be the site of the wound, independently of the influence of sepsis or gangrene. It has been noted by us that a fatal issue is more common when the body, as distinguished from the limbs, has been wounded. Thus, as will be seen in Table II., out of 115 fatal cases, 61, or 53 per cent., were cases in which the

TABLE II.—*The Position of the Wounds in Reference to the Mortality.*

—	Body.	Limbs.
Fatal: 115 cases ...	61 (53%)	54 (47%)
Recovered: 42 cases ...	18 (43%)	24 (57%)

Note.—When wounds occurred both on the body and the limbs the case is counted only under the heading "body."

wound or some of the wounds involved the head or trunk, the balance of 54 cases, or 47 per cent., being wounds of a limb or limbs. On the other hand, of 42 cases which recovered 18, or 43 per cent., were wounds of the body, the remaining 24 recoveries, 57 per cent. of the whole, having received wounds of the legs or arms only. The difference in these figures, though not very marked, appears suggestive, and the heavier mortality of the body cases may not improbably be related to the shorter distance which the toxin has to travel in order to reach the spinal cord and the nervous centres.

THE INCUBATION PERIOD.

The interval which elapsed between the wound and the first evidences of tetanus was recorded in 157 cases and a curve has been constructed, similar to that in Sir David Bruce's papers, that the experience in France may be contrasted with that at home. The average incubation period of all the cases was 12·03 days. Of the fatal cases, 115 in number, the average period was 10·7 days, and of the 42 recoveries it was 14 days. This confirms once again the general experience that the shorter the interval between the wound and the attack the poorer the chance of the patient. At the same time, this difference is less marked than might have been expected, being only a fraction above three days, and it corresponds closely to the figures reported by one of us earlier in the war, where the difference was even smaller, 2·74 days. Comparing our curve of the incubation periods with that of the home cases they appear very similar, except that the peak of the curve in France is reached at an earlier day than in England, the eighth as contrasted with the eleventh. This is only what might have been anticipated as a larger proportion of the early and the acute cases fall to us. The shortest incubation period mentioned—two days—occurred in two instances, but in one of these there was an element of doubt as to the exact day of wounding. The other was a slight case which recovered, the presumed source of infection having been a small cut on the index

finger. On the other hand, cases of latent or delayed tetanus are naturally more common in home hospitals, the two in our list with the longest recorded intervals after wounding being, respectively, 52 days and 90 days. Each of these was fatal; the latter was presumed to have originated from an abrasion of the elbow, and in the case of the former an operation had been performed 11 days before the onset of the symptoms of tetanus.

As regards this interesting subject of delayed tetanus, in which it is to be presumed that spores remain undestroyed in the tissues till they are in some way stimulated to germination, we have 13 cases in our series in which the

Curve of the incubation period.

disease did not make its appearance until 21 days or more had elapsed. This may perhaps be assumed to be the limit of the normal incubation period, although the phrase is an awkward one to employ in the case of a bacterial disease in which the germs are introduced as spores which, theoretically, may lie dormant but living in the tissues for an indefinite time. Of these 13 cases, 8 died and 5 recovered. The figures are small, but the recovery rate in this group compares favourably with that of the whole series. The average incubation period of the 8 fatal cases was 36·3 days and that of the 5 recovered cases 29·4 days.

INFLUENCE OF OPERATION BEFORE THE ONSET OF TETANUS.

Table III. shows a list of the 34 cases in which operative interference of a grave nature had been resorted to prior to the development of the first symptoms of tetanus. Of these 34 cases 26, or 76·5 per cent., died, while 8 recovered, a recovery rate of 23·5 per cent. In 4 cases the onset of the tetanus occurred on the day following the operation and in another 4 cases on the second day after operation. In three instances the initial prophylactic subcutaneous dose had been repeated, in two of them 500 units being given a week after the first one. The third case received a second 500 units 4 days after the first and 1500 units 11 days later, on the day of the operation. Of these 3 cases 2 died and 1 recovered, but in the two fatal cases death was not considered as being primarily due to tetanus. The case which had received the three prophylactic doses died, but death was considered to have been due to sepsis and inanition; there had been no convulsions for 6 days before death. Out of 9 cases where death occurred within 3 days of operation 7 were amputation cases; in the 2 remaining ones the wounds and the operations involved the thorax. On the other hand, out of 8 recoveries 3 only were amputations, and only in one case was the thorax involved.

It may be noted that 34 out of our 160 cases fall to be described in this category, as contrasted with the 15 cases out of a total of 195 shown on Sir David Bruce's last communication. This disproportion is readily understandable as these grave operations are naturally demanded more often, and at an earlier moment, in France than in the case of wounded men whose condition was considered such that they could bear the journey to England without undue risk.

INFLUENCE OF OPERATION AFTER THE ONSET OF TETANUS.

The practice of operating after tetanus has declared itself appears to be dying out in France. Table IV. deals with only 9 such cases, and no case of this nature has been reported to us since the end of September. Of the 9 cases 7 died and

2 recovered, a case mortality of 77.7 per cent. Of the 2 cases which were most quickly fatal—viz., 1 day and 1½ days—it may again be remarked that each was a body wound; the operations apparently involved much manipulation and may thus have opened up fresh channels

TABLE III.—Occurrence of Tetanus after Operative Interference with the Wound.

No. of case.	Onset of tetanus.		Nature of wound.	Nature of operation.	Recovered or died.	Duration of disease in days.
	Days after wound.	Days after operation.				
J. 13	8	1	Leg.	Supracondylar amp.	D	1
J. 15	11	7	Back, face, hands, thigh, legs (bomb).	Incisions. Removal of necrotic tissue.	D	19
J. 21	8	5	L. thigh, large flesh wound; frac. femur.	Amp. middle thigh.	D	1
J. 22	18	11	Penetrating chest, L.; empyema.	Resection.	D	7
J. 23	6	3	Shrapnel wd. R. arm and fingers, L. arm, both legs, and buttocks.	Exploration and drainage.	D	4
J. 25	21	9	Scalp, finger, thigh, R. arm and elbow.	Ligature brachial for sec. hæmorrhage.	D	7
J. 26	8	2	L. shoulder, R. thigh.	Amp. at shoulder-joint.	D	2
J. 30	12	10	L. forearm. Severe flesh wounds.	Amp. at shoulder.	R	—
A. 11	14	4	Chest. Back.	Drainage of empyema.	D	5
A. 23	9	3	L. thigh and leg. Fracture. R. leg lacerated.	Amp. L. leg above knee. Free excision of muscle.	D	2
A. 24	10	2	Post. thoracic. Hæmothorax L.	Aspiration.	D	1
A. 26	15	12.1	Dorsum foot, involving bones.	Excision and removal of bone (1); amputation (2).	D	4
A. 27	12	8	G.S.W. chest, penetrating lung.	Extraction of F.B. chest.	D	4
A. 35	35	32	Frac. femur into knee-joint.	Excision and drainage of joint.	R	—
A. 29	26	16	Penetrating chest. Cmpd. fract. of forearm.	Resection for empyema.	R	—
S. 1	6	2	R. shoulder, upper arm.	Cleansing of arm wound.	D	6
S. 7	14	11.5	G.S.W. L. leg. Post. and outer aspect.	Excision and drainage. 1. Removal of F.B.; drainage. 2. Knee-joint reopened.	D	6
S. 14	8	5	L. leg shot away below knee-joint. R. leg and ankle also wounded.	Amputation.	D	3
S. 18	52	11	Cmpd. fract. L. humerus.	Amp. for severe sec. hæmorrhage.	D	4
S. 24	8	1	G.S.W. L. hand.	Amputation.	D	3
S. 44	12	6	Lower part of back, non-penetrating; also wound neck.	F.B. removed neck (2).	D	4
S. 47	21	16	R. leg, L. thigh, R. arm, several back.	Amp. R. thigh.	R	—
O. 3	15	12.6	Shell wd. R. buttock. F.B. lodged in ileum.	1. Excision. 2. Removal of F.B.	D	13
O. 10	26	23	L. leg, thigh, and foot; frac. tibia and metatarsal. F.B. in cornea.	Amp. thigh, upper third.	D	2
O. 11	17	16.8	G.S.W. both legs.	1. Amp. upper 3rd L. thigh. 2. Opening up of stump.	D	13
O. 19	11	6	G.S.W. head, L. temporo-maxillary joint.	Trephine. F.B. removed.	R	—
O. 20	3	0	G.S.W. R. thigh.	Opened up.	R	—
O. 22	7	4.2.1	G.S.W. L. chest.	1. Aspiration. 2. Ditto. 3. Rib resection.	D	2
O. 24	25	10	Both legs, R. knee and abdominal wall.	Drainage.	D	9
O. 29	18	14.10	Cmpd. fract. L. upper arm.	1. Cleansing, drainage. 2. R. arm incisions. L. arm disarticulation at shoulder.	D	11
O. 31	6	4.2	Cmpd. fract. L. ulna, two large dirty wds. Two large dirty wds. L. calf.	1. F.B. removed. 2. Cleansing. Removal F.B.	D	4
O. 35	43	36	Penetrating R. thigh. Commin. frac. femur.	Post. wound enlarged for drainage.	D	11
O. 41	44	9	Cmpd. fract. leg.	Amp. below knee.	R	—
O. 43	9	4	Large, over R. scalp. Small, over R. lat. dorsi.	Incision. Drainage.	R	—

for the absorption of toxin by a short route. Among the 7 deaths there were 3 amputations, but, on the other hand, both of the recoveries were also amputation cases.

The figures dealt with in these two tables III. and IV. are too small to throw fresh light on a side of the problem which has been much discussed, but we have no doubt as to the wisdom of giving a sufficient prophylactic dose a short

time before a contemplated operation, and we believe that it is generally agreed to be wise to refrain from any avoidable disturbance of the wound, or anything in the nature of a severe operation, once tetanus has declared itself, at least

TABLE IV.—Operative Interference after Appearance of Tetanus.

No. of case.	Onset of tetanus. Days before operation.	Nature of wound.	Nature of operation.	Recovered or died.	Duration of disease in days.
J. 4	0	G.S.W. R. shoulder, frac. scap.	Incision, cleansing.	D	1½
J. 7	0	Shell wound R. thigh, frac. femur.	Amp. on appearance of symptoms.	D	(?)*
J. 10	1	Perf. L. leg above ankle.	Amputation.	R	—
J. 11	1	L. knee-joint.	Amputation.	D	(?)*
J. 16	0	G.S.W. R. upper arm.	Incision, drainage.	D	3
J. 29	2	G.S.W. L. foot.	Amputation through calf.	R	—
A. 31	3	Thigh.	Removal F.B. and drainage.	D	8
S. 3	0	Near R. ant. sup. spine, frac. of ilium.	Free opening up of wound.	D	1
S. 5	3	R. tibia cmpd. frac., wounds R. leg and perineum.	Femoral artery tied.	D	5

* Not stated.

until there is some sign of abatement of the symptoms and until a sufficient amount of antitoxin has been administered. The latter question will be mentioned again below.

THE PROPHYLACTIC USE OF TETANUS ANTITOXIN.

Although, as has been said, the influence of this upon the general incidence of tetanus in the wounded must be left on one side, there remain some points in connexion with it which are of interest and may be discussed without indiscretion.

It is, of course, well known that the earlier the preventive dose is given after the receipt of the wound the more likely is it to be of use. At the same time there is little positive information as to the effects of delay. An effort was therefore made to obtain precise details as to the number of hours which had elapsed between wound and injection. This was obtained in a considerable proportion of the 160 cases—viz., 66. It would have been easy to group for analysis a still larger number than this if one had been content to include cases in which the replies gave one a reasonable certainty that the dose had been given within 24 hours, but only those have been accepted in which a definite statement was forthcoming as to the fact of inoculation, the dosage, and the number of hours after the wound at which the dose was given.

Of the 43 cases which received within 24 hours a preventive dose of 500 or more units—less is never given—62.7 per cent. were fatal and 37.2 recovered. On the other hand, of 23 cases in which the giving of the antitoxin was, for one reason or another, delayed beyond 24 hours, 86.9 per cent. died and only 13 per cent. recovered. These figures are given for what they are worth, and it should be borne in mind that delay in giving the preventive inoculation is almost always caused by the impossibility of removing the wounded man from the place where he was hit till military conditions permitted. Such cases are therefore specially liable to gangrene and to the more severe forms of septic trouble.

These 66 cases are further analysed in Table V. to see whether there was any noticeable correlation between the time of administration of the preventive dose, the average size of this dose and the length of the incubation period. The chief points which emerged from this were that the average incubation period of the recovery cases who got their preventive dose within 24 hours is longer than that of the other classes, and that of those whose dose was delayed, and who yet recovered, the average size of the dose given was large—viz., 915 units.

No prophylactic dose was given in 15 of the cases, and 9 of these died—i.e., 60 per cent. It is to be noted, however, that of the 6 who recovered 5 were instances of men whose injuries, being of the nature of scratches or abrasions, were so slight that they did not report sick, and hence received no dose of serum. Others of those who received

no serum were of that unlucky class who have only been picked up some days after their injury, having lain untound in some shell-hole or perhaps in such a portion of "No man's

TABLE V.—Correlation between the Amount of Prophylactic Dose given, the Time of Administration, and the Incubation Period.*

	Interval between wound and prophylactic dose	Number of cases.	Percent- age.	Average prophylactic dose	Average incubation period.
Fatal cases, 47	Under 24 hours	27	57.4	655 units.	10.6 days.
	Over 24 "	20	42.6	585 "	10.5 "
Recovered cases, 19	Under 24 hours	16	84.3	630 "	14.7 "
	Over 24 "	3	15.7	915 "	11.0 "

* Incubation period in all cases is reckoned as the interval between the wound and the onset of tetanus, whether there was an intermediate complicating factor, such as an operation, or not.

land" as made it impossible to reach them. Their condition on rescue has sometimes been so critical that the medical officer did not consider it wise to give an inoculation.

THE THERAPEUTIC USE OF TETANUS ANTITOXIN.

The "questionnaire" completed in all cases of tetanus was principally designed to obtain accurate information upon the details of antitoxin administration, the number, size, and route of introduction, and the dates of each dose being asked. This information has been given in every case and has formed the subject of close study from as many different points of view as possible. Our thanks are due to the officers who furnished us with these details, collected often under conditions of great stress. Our object, it need hardly be said, was to search the collected results for any indications for or against a particular system of dosage or a particular channel, or combination of channels, of administration of the antitoxin.

Of the 160 cases, all but three, each of them fatal, were treated with antitoxin, so the tables now to be discussed deal with 157 cases.

The number of possible variations in the treatment adopted, as well as the various complications already alluded to, make it a very difficult matter to arrive at clear-cut answers to any given question, and had there been more general agreement on the usefulness of antitoxin in the treatment of declared tetanus and on the best methods of employing it, we should have preferred to wait till more material had become available for analysis. Still, certain points have rather forced themselves upon our notice in our inquiry into the returns, and we believe them to be of sufficient importance to put on record forthwith.

The paper of Sir David Bruce, dealing as it does with a further 175 cases treated with antitoxin in home hospitals, forms a ready means of multiplying experience on certain points, and we shall frequently avail ourselves of the opportunity thus given of comparing our respective experiences and conclusions.

In examining the results of a certain line of treatment we have, as already said, been content to accept as the criterion of success or failure the survival or death of the patient, leaving out of consideration any statement that death was due in the main to some other cause than tetanus.

Table VI. shows the cases distributed in accordance with the total amount of antitoxin which they had received, being arbitrarily divided for this purpose into eight classes. In each group is shown the number of deaths, the case mortality, and the channels of administration by which the serum had been given. As will be seen, there are no fewer than 15 possible combinations of the four routes which we have had under consideration, and there are instances of each of these combinations having been employed. We have taken no account of a few cases in which antitoxin was said to have been given by the mouth or by the rectum, and there has been no report of its local application to the wound. For the sake of brevity we shall in our tables employ an initial letter to signify the particular route, thus "T" = the intrathecal method, "V" = the intravenous, "S" = the subcutaneous, and "M" = the intramuscular. We shall leave the tables largely to speak for themselves, when they have anything to say, confining our comments to such points as appear to us of significance or as needing further explanation or emphasis.

As regards Table VI., the chief point sought was any broad indication of the effects of the total dosage of anti-

toxin. In studying this point we at one time divided our cases accordingly as they had received a total dosage of less or more than 20,000 units. Although we decided later to abandon this method for the succeeding tables as too complicating, we may return to it here as bringing out the

TABLE VI.—Showing the Total Number of Cases Treated by Serum.

Dose (in units).	No. of cases.	Died.	Case mortality.	Methods of administration *														
				T.	V.	S.	M.	T.V.	T.S.	T.M.	V.S.	V.M.	S.M.	T.V.S.	T.S.M.	V.S.M.	T.V.M.	T.V.S.M.
Below 500	5	4	80%	3	—	2	—	—	—	—	—	—	—	—	—	—	—	—
501- 1,000	3	3	100%	2	—	1	—	—	—	—	—	—	—	—	—	—	—	—
1,001- 5,000	43	42	85%	12	5	16	2	2	—	—	—	—	—	—	—	—	—	—
5,001- 10,000	25	16	64%	6	—	4	1	3	8	2	—	—	—	—	—	—	—	—
10,001- 20,000	34	26	76%	2	1	2	1	5	5	1	—	—	—	—	—	—	—	—
20,001- 50,000	25	16	64%	—	—	1	1	4	3	2	—	—	—	—	—	—	—	—
50,001-100,000	14	6	43%	—	1	1	—	3	1	1	2	—	—	—	—	—	—	—
Above 100,000	2	2	100%	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—
Totals... ..	157	115	73.7	25	7	7	4	14	28	13	4	2	1	20	4	1	5	2

* T. = Intrathecal. V. = Intravenous. S. = Subcutaneous. M. = Intramuscular.

The cases are grouped according to the total dosage given, together with the case mortality. The groups are subdivided to show how many cases fall into each one of the 15 possible combinations.

desired point somewhat more clearly. As will be seen, the first five classes, those in which the total dosage had been below 20,000 units, comprise 116 cases, of whom 91 died, a case mortality of 78.4 per cent. The remaining 41 cases received more than 20,000 units, and of them 24 died, a case mortality of 58.5 per cent. There is therefore a balance of 20 per cent. in the favour of the larger dosage. Turning to a somewhat similar table in connexion with the cases treated in home hospitals, and dividing the 175 cases therein analysed into similar groups, below and above a total dosage of 20,000 units, we find that of 108 cases in the small-dose category, 61 died, a case mortality of 56.4 per cent., while of the 67 cases in the large-dose class only 21 died, a case mortality of 31.3 per cent. The balance here in favour of the larger total dosage is 25 per cent., a difference even more pronounced than in our own series.

Taken together, we think there can be little doubt that they demonstrate the better results obtainable from the higher dosage. We have very closely scrutinised our cases to see what influence certain obviously possible fallacies might have had upon this conclusion. For instance, it is possible that relatively small dosage may have been adopted of necessity because the case was rapidly fatal, either from tetanus or a complication; or, on the other hand, the case may have been so slight that the dosage was originally small and was rapidly abandoned. Such cases undoubtedly occur, but against them may be set, unfortunately, the equally certain fallacy that even in severe and prolonged cases the dosage recorded has, in our view at least, been altogether inadequate, owing to an obvious unbelief in the value of specific treatment. These, and some other disturbing factors, we think tend to cancel one another and we do not consider that they lessen materially the significance of the figures just quoted.

TABLE VII.—Showing the Total Number of Cases Treated by Serum (with or without Non-specific Treatment), together with the Number of Deaths and the Case Mortality. The Table also shows the Number of Cases treated by any one of the Four Available Routes alone or in Combination with One or More of the other Three Routes.

Methods of administration.	No. of cases.	No. of deaths.	Case mortality.	Methods of administration.	No. of cases.	No. of deaths.	Case mortality.
			Per cent.				Per cent.
T.	25	21	84	S.M.	1	1	100
V.	7	7	100	T.V.S.	20	17	85
S.	27	15	55	T.S.M.	4	1	25
M.	4	3	75	T.V.M.	5	3	60
T.V.	14	11	78	V.S.M.	1	1	100
T.S.	28	21	75	T.V.S.M.	2	1	50
T.M.	13	9	69				
V.S.	4	4	100				
V.M.	2	0	0				
				Totals	157	115	73

The next table, VII., sets out the cases treated by antitoxin and it shows for each route or combination of routes by which the serum was given, the number of cases, the deaths,

and the case mortality. The uneven size of the groups, and their very number, make evident the futility of any attempt to form conclusions from a consideration of the degree to which the case-mortalities are above or below the mean rate of the whole 157 cases. A better opportunity is afforded by a consideration of the series of Tables VIII., IX., X., and XI., in which the cases are grouped on a different system. Here we have placed together all cases in which one particular route, whether alone or in combination with others, formed part of the system of treatment, a separate table being devoted to each of the four—"T.," "V.," "S.," and "M." Each of these will now be briefly considered.

Table VIII. deals with the intrathecal route, employed either alone or combined with others. It was used alone in 25 cases, with a mortality of 84 per cent., and this, with the single exception of the combination "T.V.S.," is, it will be noted, the highest rate shown in the table. Looking to Sir David Bruce's figures we see that "T." was used alone in 7 cases, of which 5 died, a mortality of 71.4 per cent., the highest mortality of any group analysed in his paper. So far this does not impress one favourably. Turning to the use of "T." in combination with others, the only other point we shall call attention to is that in each of the four groups

TABLE VIII. shows all Cases Treated by the Intrathecal Route, and TABLE IX. shows all Cases Treated by the Intravenous Route, either Alone or in Combination with One or More of the other Routes, together with the Number of Deaths and the Case Mortality.

Table VIII.—Intrathecal Route. Table IX.—Intravenous Route.

Methods of administration.	No. of Cases.	No. of deaths.	Case mortality	Methods of administration.	No. of Cases.	No. of deaths.	Case mortality
			Per cent.				Per cent.
T....	25	21	84	V....	7	7	100
T.V....	14	11	79	V.T....	14	11	79
T.S....	28	21	75	V.S....	4	4	100
T.M....	13	9	69	V.M....	2	0	0
T.V.S....	20	17	85	V.T.S....	20	17	85
T.S.M....	4	1	25	V.T.M....	5	3	60
T.V.M....	5	3	60	V.S.M....	1	1	100
T.V.S.M....	2	1	50	V.T.S.M....	2	1	50
Totals...	111	84	75	Totals...	55	44	80

TABLE X. shows all Cases Treated by the Subcutaneous Route and TABLE XI. shows all Cases Treated by the Intramuscular Route, either Alone or in Combination with One or More of the other Routes, together with the Number of Deaths and Case Mortality.

Table X.—Subcutaneous Route.

Table XI.—Intramuscular Route.

Methods of administration.	No. of cases.	No. of deaths.	Case mortality	Methods of administration.	No. of cases.	No. of deaths.	Case mortality
			Per cent.				Per cent.
S....	27	15	55	M....	4	3	75
S.T....	28	21	75	M.T....	13	9	69
S.V....	4	4	100	M.V....	2	0	0
S.M....	1	1	100	M.S....	1	1	100
S.T.V....	20	17	85	M.T.S....	4	1	25
S.T.M....	4	1	25	M.T.V....	5	3	60
S.V.M....	1	1	100	M.V.S....	1	1	100
S.T.V.M....	2	1	50	M.T.V.S....	2	1	50
Totals...	87	61	70	Totals...	32	19	59

showing the lowest mortality the intramuscular route has formed a part of the combination. The moral would appear to be that if one employs the thecal route at all it is better to use it in combination than alone. This is even more strikingly illustrated in the home figures, where the relative death-rates are 71.4 per cent. and 46.7 per cent.

Table IX. deals in a similar way with the intravenous route alone or combined. Of 55 cases in the group 44 died, a mortality of 80 per cent., and we have the striking fact brought out that no case treated by this channel alone recovered. In the home figures the mortality in 7 cases treated by "V." alone was 57 per cent., the second highest in the list. Looking again at the results of the various combinations of "V." with other channels, one again notes that the three lowest mortalities are in groups in which "M." appears.

Table X. shows the subcutaneous route alone and in combination with others. Of 87 cases in which this route

was employed the general case mortality was 70 per cent. When used alone, in 27 cases the mortality was considerably lower, 55 per cent., and here the apparent effect of combining this route with others is bad, except in two particular combinations, into each of which "M." again enters. In the home figures the mortality from cases treated by "S." alone was 50 per cent., but there is no information as to the frequency with which it was employed in combination.

Table XI., the last of this group of four, deals in similar fashion with the intramuscular route. Of 32 cases in which it played a part 19 died, a case mortality of 59 per cent., the lowest figure by 11 per cent. of the four tables. The groups are too small here to afford much information, and, so far as the figures go the mortality resulting from its use alone, 75 per cent., contrasts unfavourably with the mean rate of 59 per cent. This group, however, deals with but 4 cases and may be usefully supplemented by the home figures, which show that of 8 cases treated by this method alone only 1 died, a mortality of 12.5 per cent. Combining these 8 cases with our own 4 we have 4 deaths out of 12 cases, a mortality of 33.3 per cent., which is by far the lowest recorded in either series for the results of a single channel antitoxin treatment.

We fully appreciate the many pitfalls into which one may stumble in searching for truth among small figures dealing with cases presenting so many complicating factors; but, so far, our examination of them has given us some strong impressions, all the stronger in that they were by no means anticipated. 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 employment of the subcutaneous and intramuscular channels, particularly the latter. The evidence for and against the intravenous method also leaves one with a feeling of suspicion, particularly in view of the fact that all of the cases treated by this channel alone died.

EFFECTS OF THE DOSAGE OF ANTITOXIN EMPLOYED BY THE SEVERAL ROUTES.

It is obvious, however, that, in considering the results of the various combinations of specific treatment dealt with in the last four Tables VIII., IX., X., and XI. there is a factor of importance which is not disclosed by them, but which it is essential to consider. It is not enough to treat all cases as alike that have received serum treatment by the same combination of routes, we must study the amount and frequency of the dosage by each route if we are to reach a fairer judgment of results. This has accordingly been done, and every individual case has been closely studied from this point of view. A table showing the full details of every dose given in the 157 cases was constructed, but as this would be too elaborate to reproduce we have constructed Tables XII., XIII., XIV., and XV., which, while repeating the classification of cases adopted in Tables VIII., IX., X., and XI., show, in addition, the average amount of antitoxin given by each route in each group of cases. This table enables one to grasp more readily the relative importance to attach to each route in any given combination of routes, and to see how this factor of dosage compares in the cases which recovered and those which died.

Table XII. displays all cases in which the intrathecal route played a part. Contrasting the average dose given by the thecal route in the fatal and recovered cases respectively and in each combination, it will be seen that there is no regularity; in some instances more had been given in the recovered cases, in others less. Looking, then, at the venous fraction, here, too, we see no regularity; a larger dosage by the veins seems in some cases to have been beneficial, in others the reverse. But when we consider the remaining fractions, subcutaneous and intramuscular, in each group into which they enter we notice in all cases that the dosage has been higher, usually much higher, in the recovery cases than in the fatal ones. It should be noted, however, that neither in this nor the succeeding three tables of the series do we attempt to draw any inferences from the two cases in class "T.V.S.M.," the employment of all four routes appearing to us to render any attempt of this sort futile.

Table XIII. deals in similar fashion with the intravenous route in all combinations. Analysis in this group is difficult, as in no less than four of the combinations we have

either no deaths or no recoveries, as well as the group "V.T.S.M.," of which we take no notice. The two groups most suitable for contrast, on account of the number of cases, are "V.T.," where the recovered cases show a larger

TABLE XII. shows Cases Treated by the Intrathecal Method and TABLE XIII. shows Cases Treated by the Intravenous Method, either Alone or in Combination with One, Two, or Three other Methods. Contrast of the Average Amounts of Antitoxin used in the Fatal and Recovery Cases.

Table XII.—Intrathecal Method.

Table XIII.—Intravenous Method.

Method of administration.	Number of fatal cases.	Average amount used by each route.	Number of recoveries.	Average amount used by each route.	Case mortality.	Method of administration.	Number of fatal cases.	Average amount used by each route.	Number of recoveries.	Average amount used by each route.	Case mortality.
T.	21	3,810	4	7,250	Per cent 84	V.	7	13,890	0	—	Per cent 100
T.		4,470		3,000		V.		14,345		24,000	
V.	11	14,345	3	24,000	79	T.	11	4,470	3	3,000	78
T.		4,050		8,000		V.		9,875		—	
S.	21	6,950	7	18,000	75	S.	4	18,000	0	—	100
T.		4,970		12,560		V.		—		60,000	
M.	9	6,500	4	27,560	69	M.	0	—	2	24,000	0
T.		6,430		3,750		V.		12,535		13,500	
V.	17	12,535	3	13,500	85	T.	17	6,430	3	3,750	85
S.		7,985		25,500		S.		7,985		25,500	
T.		7,500		4,300		V.		15,500		5,250	
S.	1	3,000	3	6,170	25	T.	3	4,170	2	7,000	60
M.		6,000		11,800		M.		8,330		12,750	
T.		4,170		7,500		V.		500		—	
V.	3	15,500	2	5,250	60	S.	1	1,000	0	—	100
M.		8,330		12,750		M.		3,000		—	
T.		18,000		8,000		V.		100,000		14,000	
V.		100,000		14,000		T.		18,000		8,000	
S.	1	50,500	1	17,500	50	S.	1	50,500	1	17,500	50
M.		34,000		4,500		M.		34,000		4,500	
Totals	84		27		75	Totals	44		11		80

thecal dose was given, but three times the subcutaneous dose, as contrasted with the dosage given in the 17 fatal cases.

Table XIV., dealing with the dosage of the subcutaneous route, alone or combined, brings out more clearly than the others the observation that, in all groups in which we are able to make a comparison between the dosage in the recovered and in the fatal cases, a much higher average dose has been given to the cases which lived. This is particularly noticeable in the group treated by the subcutaneous method alone, where the average dose has been $4\frac{1}{2}$ times higher in the cases which recovered, and in the two other fair-sized groups, "S.T." and "S.T.V.," in which the subcutaneous dose was respectively $2\frac{1}{2}$ and $3\frac{1}{2}$ times greater in the recovery cases. In all, this table impresses us with the value of high dosage when the subcutaneous route is employed.

Table XV., the last of this series, shows the average dose of antitoxin employed in all combinations in which the intramuscular route was used. The various groups in this category are, on the whole, too small to extract from them much guidance in this matter of dosage, but it will be seen that in the largest group, "M.T.," dealing with 13 cases, about four times as much antitoxin was given intramuscularly in the recovered cases as in those which died. In the "M.T.S." cases, in which 3 recovered and 1 died, the intramuscular dose was twice as great in those who lived. On the other hand, in the cases treated by intramuscular injections alone, of which 3 out of 4 were fatal, the only case which recovered received less than half of the average dose given to the fatal cases. On the whole, although the figures are small, we get the same impression here as in the instance of the subcutaneous route—that the apparently favourable effect of employing this channel is associated with a proportionally high dosage.

On regarding these four tables from a general point of view, and without attempting to draw from them more than may reasonably be inferred, 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.

The last table which we shall give, Table XVI., was designed in an attempt to visualise and contrast the results obtained by single-route administration of antitoxin with the results of using that particular route in combination with others.

Looking at the intrathecal results, we see that the case mortality is 10 per cent. higher when this route is used

TABLE XVI.—Comparing and Contrasting the Results Obtained by Each Individually, with those Obtained by that Route in Combination with One or More Others.

	Total cases treated.	Average dosage employed.	Died.		Recovered.		
			Number of cases.	Case mortality.	Number of cases.	Recovery rate.	Average dosage.
Intrathecal route only	25	4,360	21	84%	4	16%	7,250
Intrathecal cmbd. with other routes.	86	5,680	63	73.2%	23	26.7%	7,060
Intravenous route only	7	13,890	7	100%	0	0	—
Intravenous cmbd. with other routes.	48	16,966	37	77%	11	23%	23,360
Subcutaneous route only	27	6,470	15	56%	12	44%	4,500
Subcutaneous cmbd. with other routes	60	11,780	46	77%	14	23%	17,036
Intramuscular route only	4	6,375	3	75%	1	25%	3,000
Intramuscular cmbd. with other routes	28	14,650	16	57%	12	43%	18,640

alone, and also that the total dosage given by the thecal route in the fatal cases was considerably higher in the group in which this channel was employed along with others than when it was employed alone. It was remarked, however, that a considerable proportion of the 21 fatal cases treated by the single-route method were exceptionally severe cases of gunshot injuries. In 9 of them death was

TABLE XIV. shows Cases Treated by the Subcutaneous Method and TABLE XV. shows Cases Treated by the Intramuscular Method, either Alone or in Combination with One, Two, or Three other Methods. Contrast of the Average Amounts of Antitoxin Used in the Fatal and Recovery Cases.

Table XIV.—Subcutaneous Method.

Table XV.—Intramuscular Method.

Method of administration.	Number of fatal cases.	Average amount used by each route.	Number of recoveries.	Average amount used by each route.	Case mortality.	Method of administration.	Number of fatal cases.	Average amount used by each route.	Number of recoveries.	Average amount used by each route.	Case mortality.
S.	15	2,450	12	11,500	55	M.	3	7,500	1	3,000	75
S.		6,950		18,000		M.		6,500		27,560	
T.	21	4,050	7	8,000	75	T.	9	4,970	4	12,560	69
S.		18,000		—		M.		—		24,000	
V.	4	9,875	0	—	100	V.	0	—	2	60,000	0
S.		60,000		—		M.		60,000		—	
M.	1	60,000	0	—	100	S.	1	60,000	0	—	100
S.		7,895		25,500		M.		8,330		12,750	
T.	17	6,430	3	3,750	85	T.	3	4,170	2	7,500	60
V.		12,535		13,500		V.		15,500		5,250	
S.		3,000		6,170		M.		6,000		11,800	
T.	1	7,500	3	4,300	25	T.	1	7,500	3	4,300	25
M.		6,000		11,800		S.		3,000		6,170	
S.		1,000		—		M.		3,000		—	
V.	1	500	0	—	100	V.	1	500	0	—	100
M.		3,000		—		S.		1,000		—	
S.		50,500		17,500		M.		34,000		4,500	
T.		18,000		8,000		T.		18,000		8,000	
V.	1	100,000	1	14,000	50	V.	1	100,000	1	14,000	50
M.		34,000		4,500		S.		50,500		17,500	
Totals	61		26		70	Totals	19		13		59

venous dose and a smaller thecal one than the fatal cases, and Group "V.T.S.," in which, while the venous average dose is approximately equal in fatal and recovered cases, we are struck by the fact that in three recoveries only half the

attributed by the reporting officer to causes other than tetanus. Thirteen of them died within 24 hours of the first appearance of tetanic symptoms. Of the recovery cases all were noted as being either slight or localised and none of them reached the stage of trismus.

As regards the intravenous channel, attention has already been directed to the fatal issue in all cases treated by this method alone. The high dosage employed will be remarked, as well as the fact that the average dose given to the recovered cases in whom this channel had been used in combination with others was highest of all. In examining the individual records of the 7 fatal cases treated by the venous route only it was remarked that, although they were all severe wounds, the antitoxin was not persisted in in several, though time allowed for its repetition. In only 2 out of the 7 was the dose above 5000 units.

The subcutaneous route employed alone shows the lowest mortality—viz., 56 per cent. Of the 15 fatal cases 7 were severe wounds, in which death was not attributed directly to the tetanus. The dosage employed in these fatal cases was also remarked upon as being very small, in only one of them was it over 3000 units and most received 1500 units or less. Of the 12 recoveries in the single-route group 6 were either localised or slight, but the dosage only fell below 3000 units in one case, which received 500. The wounds in this group were, on the whole, slight.

Too few cases were treated by the intramuscular route alone to allow of effective contrast with those in which this method was associated with others. Of the 3 fatal cases, 2 were specially severe wounds and the intramuscular dosage was moderate. The recovery case, although severe, was, on the other hand, given 3000 units only. The high average dosage given into the muscles in the 12 recovery cases in the combined group, 18,640 units, is also noteworthy.

SUMMARY.

The above analysis of these tables dealing with the therapeutic employment of tetanus antitoxin leaves, we are fully aware, much to be desired, and, at any other time than this, we should have greatly preferred to postpone this article until our material was larger. The importance and urgency of the subject, however, form our justification, and we shall now proceed to summarise the impressions we ourselves have gathered, trusting that we have presented the available facts in such a way that any who wish may do the same.

Our general conclusions would place the alternative channels of administration of the antitoxin in the following order of merit—intramuscular, subcutaneous, intrathecal, and intravenous. Let us consider each separately, emphasising the points of experience or theory which have influenced our judgment. Taking the intravenous route first, as we have placed it last, we are in full agreement with the recommendation of the Tetanus Committee in their revised Memorandum, that this route should not be used; not only does it introduce a risk of anaphylactic shock, from which other methods are practically free, but it appears to us from our records that it has done little, if any, good in treatment. It seems improbable that, even when very large doses are injected into the veins, the antitoxin is likely to be brought to a point at which it is most wanted in a sufficiently concentrated form. Of what is injected only a small fraction can possibly be utilised, and, further, we do not think that the effects of the antiseptic which is mixed with most brands of antitoxin can altogether be neglected when large and repeated doses are injected by this channel.

As to the intrathecal route, we are less inclined to support the recommendation contained in the Memorandum just mentioned when it says: "In a case of tetanus the first thing to do is to give an intrathecal injection of antitoxin." The study of our own cases has not impressed us at all favourably. Sir David Bruce, in his article of Dec. 2nd, considers that the evidence for and against it from his series of cases at home hospitals is not conclusive. We are inclined to go further and consider, from our own tables, and also to some extent from his, that the evidence is pretty strongly against its employment. The theoretical grounds for the adoption of the thecal route are, of course, well known, and depend chiefly on the hope that by bringing antitoxin into more or less close contact with the poisoned nerve cells of the cord we may effect a dissociation between the cell and the molecules of toxin which it has bound to itself. It is known to be very difficult to introduce antitoxin into the cerebro-spinal fluid by means of the blood-stream; hence

the direct path chosen in lumbar puncture. We shall not attempt to analyse the experimental evidence bearing upon this subject, but think it will be agreed that a considerable divergence of opinion still exists as to whether what we aim at, a dissociation of toxin from the poisoned nerve cell, is realisable in practice. The good effect of intrathecal injections of serum in some cases of cerebro-spinal meningitis has really no bearing upon this problem, because, in that instance, we are directly attacking a bacillus which we know to be present in the fluid into which we introduce our antiserum. Again, in that disease marked benefit often results from the mere evacuation of the turbid fluid which has accumulated under pressure, without even replacing it by an injection of serum.

Apart, however, from doubts as to the soundness of its theoretical basis, the method appears to us to possess some very definite disadvantages and dangers. For example, the dangers of contamination of the needle track, in spite of scrupulous precautions at the time of operation, must be very considerable in certain cases. At all events, definite comments have been made in connexion with some of our cases that thecal injections have been followed by signs of meningeal irritation, and one of us has seen specimens of cords, removed after death from tetanus, in which there was definite evidence of meningitis having followed the lumbar punctures. Again, although Flexner and others have stated that the amount of antiseptic usually added to antitoxin as a preservative is no impediment to its employment by the thecal route, we do not think that repeated injections of carbolic acid, trikresol, &c., can be altogether a negligible consideration in the case of a canal whose limiting membranes are so delicately constituted and their functions so imperfectly understood, to say nothing of possibly adding to the grave irritation already present in the adjoining nerve cells of the motor tracts owing to the action of tetanus toxin. In at least one case death followed rapidly upon a thecal dose when the patient was said to have been progressing favourably. It was attributed to anaphylactic shock.

Although we have this decided impression that the intrathecal route may be a dangerous one and do not feel its theoretical foundations to be as secure as one would like, still we have a fair number of instances in which the reporting medical officer was struck with the apparent benefit following a thecal dose, and, of course, as our tables show, it has formed a part of the treatment in 27 cases which recovered.

If it is desired to employ this method we think that its use should be very carefully watched, that exceptional care should be taken to guard against possible contamination of the canal through the needle puncture, that the serum should contain no preservative, and that it is undesirable to withdraw more than 10–15 c.c. of cerebro-spinal fluid or to replace this by a greater volume of antitoxin. It might be advisable to employ for this purpose a solution of desiccated antitoxin, which would be free from preservatives, and could be rapidly prepared under sterile conditions in the desired concentration.

The subcutaneous and intramuscular routes may appropriately be considered together, as they are essentially similar in action, each being a comparatively slow and continuous method of dosage as distinguished from the rapid introduction involved in the venous and thecal methods. While we have expressed our unfavourable impressions in respect of these rapid methods, we have in the present case received a strongly favourable impression, which is confirmed to some extent by the results obtained in the home hospitals. Hitherto these two routes have been looked on as merely supplementary to the others and as being of chief value when it was desired to maintain a moderate concentration of antitoxin in the system after the critical period was past, and with a view to warding off a possible relapse. We think, on grounds both of theory and observation, that they might be promoted to a more dignified position. We believe our records show that when these two paths of introduction have been utilised freely, and where the dosage has been sufficient, the results as regards saving of life have been more satisfactory than when they were not utilised or were used in altogether too restricted a fashion.

Turning to the theoretical aspect, we may follow for a moment the path which the toxin is believed to travel on its way to the central nervous system. It is generally accepted that it travels by way of the motor nerves, though it is still a matter of debate whether it progresses through the axis

cylinders or through the lymphatics which accompany these nerves. At all events, the general blood stream and lymph stream are considered to play but a small part. Once the tetanus spores have found conditions suitable for their germination, and the bacteria themselves are multiplying without interference in some nook or cranny of the wound, the formation of the toxin goes on continuously. It is possible that this toxin at times may accumulate locally and only upon some local disturbance of the wound does it become absorbed in quantity, producing probably a rapid and fulminating attack. At other times the toxin may be slowly but continuously taken up by the nerves, as it is formed, and this may lead to a comparatively slow onset of the disease. In either case we have then to deal with a localised factory of the toxin, which is either continuously or discontinuously absorbed along the nerves. Looking now at the possibilities of neutralising this toxin, we have in our hands a perfect antidote, of that there can be no question, and the problem becomes clear that it is an affair of trying to bring antidote and poison in contact with one another within the shortest time and under the most favourable conditions for neutralisation to take place. The alternative lines of attack are three and no more—the local factory of toxin, the line of transit of the toxin to the central nervous system, and the central nervous system itself. The first would, of course, be the ideal one to select, but, unfortunately, we cannot locate it with precision, and attempts to reach it and to deal with it by surgical measures, or by the local application of various antiseptics or oxidising agents, more often than not end in failure or in a sudden outpouring and absorption of toxin. The last, the central nervous system, is difficult to reach and, at the best, this is an attempt to recapture from the enemy a position which they have already taken and hold in great strength. The method of intrathecal injection aims at such a local assault but depends for its possible success on two assumptions—namely, that the antitoxin shall actually come into contact with the nerve cells which are poisoned and, having come into contact with them, shall be able to neutralise or withdraw from these cells the tetanus toxin which had reached them. In practice the results of this line of attack appear to us, from our own and the home cases, to be most disappointing.

The chances of success by employing the third alternative, an attack on the lines of communication, would appear more hopeful, especially if this could be done by some method which would keep up the antitoxin attack steadily and continuously on the path over which it is probable the toxin must travel. To effect this there appear to be grounds for considering that the subcutaneous and the intramuscular channels offer greater prospects of success than the intravenous method, for the reason that the dose of antitoxin thrown into the veins is immediately diluted by the whole volume of the blood and, subsequently, of the lymph, and by the time any portion of it comes round to the site where it is required it must be very dilute indeed. On the other hand, antitoxin injected beneath the skin or into the muscles is said to be absorbed but slowly, taking, it is stated, 48 hours in the case of the subcutaneous site and 24 in that of muscular. This comparatively slow rate of dispersion of the antitoxin, presumably into the blood or lymph streams, is usually held to be a disadvantage, and it is largely on this account that the more rapid methods of venous or thecal injection have been advocated as more suitable for treatment in the early or acute stages. To us it appears that this slow rate of absorption should rather be counted as a virtue, especially when the inoculations are made somewhere along the supposed path taken by the toxin in its journey from wound to cord. At all events, it seems clear that by these methods we could in a given area produce a zone of tissue bathed in antitoxin in far higher concentration than could be produced in the blood and lymph of the part by means of intravenous injections, except perhaps by immense doses frequently repeated. Further, it is probable that this antitoxin would remain available locally in considerable strength for a number of hours. On the other hand, assuming that antitoxin is absorbed from the muscles with comparative rapidity, this would be a reason for utilising that channel in order to reach the nerve-centres rapidly, through the general circulation, in cases where it was hoped to effect an early dissociation of toxin from these centres.

Should the wound be a single one, and especially if it is on a limb, we believe it would be sound practice to introduce

antitoxin, both subcutaneously and intramuscularly, somewhere astride the path which the toxin must travel on its way to the spinal cord. To do this effectually it would appear, if our ideas are correct, better to divide the dose and inject portions on each surface of the limb and also at different depths amid the muscles. Somewhere among these tissues we know the nerves run along which the poison is travelling, and the more evenly distributed our antitoxin the better would appear the chance that it may attain effective contact with the toxin and achieve our object.

We have already mentioned that the results of these two methods of introducing antitoxin appear, in the present series of cases, to have been better than those of either the intrathecal or the intravenous methods. It may be that they would have been better still if employed alone and on the lines suggested above.

Turning now to the question of dosage this appears a most difficult matter to judge. Cases recover in which the amount given has been almost ludicrously small, and others have died in spite of enormous doses. It appears to be a question of bringing the antitoxin into effective contact with the toxin. There can be no conceivable benefit in flooding the body fluids with antitoxin if this never reaches the site where it is required, and, on the other hand, quite a small dose might, by acting at the right time and in the right place, do all that was needed. There are obvious limits to the amount which one can inject intrathecally, but none by the other routes. On the whole, while admitting that we have little to guide us in the matter, we think that, if the combined subcutaneous and intramuscular routes be used, the daily dosage for the first few days should not fall below 10,000 units. If it be desired to supplement this by intrathecal injections it would appear wise to limit these to such a number of units as could be contained in 10 or 15 c.c.

We are in full agreement with all that has been said on the necessity for commencing specific treatment at the earliest possible moment and also on maintaining an effective dosage well into convalescence. The present series contained several examples of relapses occurring on the cessation of serum treatment. With regard to the recommendations of the Tetanus Committee as to watch being kept for early signs of tetanus, this is obviously of the first importance. In connexion with the present series of cases we have unfortunately received little fresh information on this point. A statement upon this point is now asked in every case, but so far has brought little to light. Practically the only early sign mentioned has been that of local contractions at or near the wound, and this has usually been followed rapidly by trismus. Some of the signs mentioned by the committee, such as pain in the wound and hardness of the tissues surrounding it, are, we fear, too common in connexion with sepsis, gas infection, &c., to possess as much value here as they might at home.

With the recommendations of the committee on the subject of repeating the initial prophylactic dose of antitoxin every six or seven days as long as there is any reason to fear tetanus, we are, we need hardly add, in the fullest accord. Instructions on this have been circulated to all concerned. Again, we agree that a preventive dose should be given prior to any secondary operation. For the reasons given above we think that it would be well to give such a dose by the combined subcutaneous and intramuscular channels, inoculating it at several points around the site of operation and at different depths of muscle on its proximal side. If time permitted this should be commenced 48 hours before the operation, but if the operation was one of urgency similar injections in the neighbourhood of the operation wound, with perhaps injection into the sheaths of prominent nerves, would appear a wise routine procedure. As far as present knowledge goes, 1500 units would be a suitable amount to give.

NON-SPECIFIC TREATMENT.

Although really outside the purpose of the present article, we may conclude with a few remarks on the replies which have reached us in connexion with this subject. Carbolic acid treatment has been almost abandoned, and few retain any faith in it. Its use was recorded in 8 cases, in strengths varying from 1-20 to 1-100. In no instance were any remarks made on its favourable influence upon the progress of the case. Magnesium sulphate also has gone out of favour, only 4 cases having been treated by this in July and 2 in September. The intrathecal route was

most often adopted. Some temporary amelioration of the symptoms and control of spasm was mentioned in 2 cases, but paralysis of the legs, lasting 24 hours, was noted in another.

Sedative drugs have been used in the great majority of cases. In order of frequency these were as follows: Chloral, bromide, morphia, chloretone, atropine, omnopon, scopolamine, alcohol, chloroform, and paraldehyde. In some cases, though but few, it was noted that one or other of these drugs had been useful in controlling spasm.

Although fully sympathising with the natural desire of the busy reader to find at the end of a paper such as this a series of "conclusions," we have abstained from them, being very conscious that we have much more to learn on every point under discussion. However, we have not hesitated to express our own views on a number of these points as we have dealt with them, and we trust that they may at least serve to rouse further interest in the specific treatment of tetanus, which we believe to be of greatest value, did we but know how to apply it aright.

MODIFIED TETANUS.

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THERE are two reasons why the subject of tetanus should be of interest at the present moment. In the first place, the disease still occurs amongst the wounded. During the months of July, August, and September, 1916, at the — General Hospital we had one case of tetanus in every 600 cases of gunshot wound. And this, of course, does not represent the full liability, for cases have occurred in patients who have been evacuated to England, and possibly at casualty clearing stations also. In the second place, a large proportion of the cases which have been seen recently have been abnormal in character, inasmuch as the muscular spasms have not become general. They have remained localised to the muscles in the neighbourhood of the original wound. Moreover, apart from the restriction of symptoms to the muscles in the vicinity of the wound, there are certain other characters which differentiate local or modified tetanus from the natural variety. These will receive attention later. In the meantime it may be remarked that in local or modified tetanus we have a new form of disease. The earliest record of a case¹ is now little more than three years old. The disease is new because its cause is new, for local tetanus is tetanus modified by the prophylactic use of anti-tetanus serum.

Forms of modified tetanus.—Cases of modified tetanus may be considered in three groups²—namely: (1) splanchnic tetanus; (2) cephalic tetanus; (3) local tetanus of the limbs. In all of these forms general spasms with opisthotonos are absent. Cases have been recorded which do not fall into any of these groups—for example, tetanus localised to the abdominal muscles. Nevertheless, these three groups will cover most of the ground and will provide sufficient material for discussion.

1. Splanchnic Tetanus.

Splanchnic tetanus³ follows upon lesions of the viscera—that is to say, penetrating wounds of the abdomen and thorax. It is nearly always fatal and the course is exceedingly rapid, so that death ensues within 24 or 48 hours from the onset of symptoms. Opisthotonos and general convulsions do not occur, the spasms being limited to the muscles of deglutition and respiration. The difficulty in swallowing is a pronounced feature, and may be so severe that the case resembles one of hydrophobia, in which case the sight, or even the mere mention, of a glass of water causes the severest pharyngeal spasm, accompanied usually by acute dyspnoea.

2. Cephalic Tetanus.

Of head tetanus there are four varieties: (1) Non-paralytic; (2) the form accompanied by facial paralysis; (3) that accompanied by oculomotor paralysis; and (4) a form in which paralysis of the hypoglossal nerves is a special feature. Of these, the non-paralytic form is said to be the least common,⁴ some motor paralysis being the rule in cases of head tetanus. And, as may be expected from its relatively wide distribution, the facial nerve is the nerve that is most commonly affected.

Head tetanus with facial paralysis.—This variety follows a wound of the face or its close neighbourhood, and is characterised by: (1) Unilateral trismus, which may become bilateral, and later on (2) difficulty in swallowing; (3) facial paralysis on the same side as the wound. The most remarkable feature is the fact that spasms occur in the paralysed muscles of the face. The explanation of this phenomenon is that there is an alteration in the conductivity of the peripheral branches of the facial nerve, which results in a partial nerve-block, sufficient to prevent the passage of voluntary impulses but insufficient to block the more powerful and pathological impulses of tetanus. The facial paralysis may persist after the other symptoms have disappeared, but ultimately, as a rule, the face recovers.

Hypoglossal form.—This form appears to be rare. As a matter of fact, in Major Kazanjian's Jaw Clinic there has never been a case, although the wounds treated there are of the kind in which hypoglossal tetanus might be anticipated.

Ophthalmoplegic form.—Ophthalmoplegic tetanus follows wounds of the orbit or its immediate neighbourhood. Ptosis is said to be the commonest symptom, but any or all of the ocular muscles, extrinsic or intrinsic, may be paralysed.

3. Local Tetanus of the Limbs.

The last abnormal form of tetanus is that which is limited to one or more of the limbs—that is to say, to one arm, or to one leg, or to both legs. These have been described as the monoplegic and paraplegic types. I do not know whether tetanus limited to the two upper extremities ever occurs. And as regards the simultaneous affection of one arm and one leg—a hemiplegic form—it is difficult to see how this could come about except as the result of simultaneous lesions of these two members.

The chief symptoms of local tetanus are clonic and tonic spasms of the wounded limbs. The clonic spasms have been described in some of the recorded cases as being accompanied by considerable pain, and as lasting for four seconds. As a matter of fact, in the four cases we have had at the — General Hospital the clonic movements have been painless and have been mere twitchings, lasting, perhaps, for half a second each. In three out of the four cases these twitchings were the first symptoms to be noticed, while in the fourth case the patient complained that his arm was stiff, and it was found that spasticity and twitchings were both present. In the two cases which survived the twitchings gradually became less frequent with the passage of time, while the spasticity became more pronounced and showed no sign of passing off so long as the patients remained under our observation.

Tetanic spasticity.—In the two fatal cases no tonic spasm at all was observed. It is quite possible that in some cases twitchings may not occur, or may escape observation, and the spasticity may then be the only material result of the tetanus. And unless attention be directed to this possibility, it is likely that the true cause of the tetanic spasticity may be overlooked, while in some recorded cases the tonic spasm has preceded the twitchings, and from these facts it is recommended that "persistent hardness in a recently wounded limb should suggest tetanus." The most likely error is to mistake tetanic rigidity for hysterical spasm, which it closely resembles. But in this connexion it is to be noted that tetanic spasticity does not pass off during sleep—at least it did not so pass off in our cases.

There is a special reflex which is indicative of tetanus, and which may be of help in diagnosing certain cases. This reflex consists of extension of the foot and leg when the sole is stimulated, and is in contrast with the normal reflex, which is a withdrawal of the foot from the stimulus. The knee is placed in a position of slight flexion while the stimulus is applied to the sole. There is another sign which Lieutenant B. S. Simmonds has pointed out, and which is elicited as follows: Suppose the leg to be affected; light touches, even the lightest with a wisp of cotton-wool, will produce reflex spasms in that leg. To bring about the spasm by stimulating the thigh, a more vigorous application is necessary; for example, tapping the skin with the fingers. And the further away from the affected part that the stimulus is applied, the more vigorous must it be to evoke reflex spasms. I have thought that respiration of automatic type is an early sign, and believe that it may precede even trismus, and be the first positively recognisable evidence of the onset of tetanus.