eight patients said "greater than" and eleven said "equal"; but even here five patients out of forty-eight indicated that A was weaker than B—that is, 10 per cent. gave what is obviously an inaccurate answer. Similarly, when Toxin A was compared with Toxin B 1 in 3,000, it is clear that A was weaker than this dilution of B, since nineteen patients said so, but six out of twenty-five patients gave an inaccurate answer. It is fair to conclude that if one is trying to compare two Dick toxins one must use a larger number of patients, probably about fifty, before one can get a reasonably accurate answer. This difficulty in matching two toxins and the necessity of using a large number of patients appears clearly from the careful work of Okell and Parish on over 150 patients reported by O'Brien (1930).

(2) Tables II and III indicate that Toxin B was less stable than A or C. Toxin B was a dilution made with the ordinary boric-borate solution originally described by Glenny, Pope, and Waddington (1928) and referred to in the *British Pharmacopoeia* (p. 463). This diluted toxin was less stable than the toxin called C in the tables, which consisted of the original toxin first diluted 1 in 4 with a stabilizing mixture, and then diluted 1 in 1,000 with the boric borate mixture. Dr. H. J. Parish of the Wellcome Physiological Research Laboratories has kindly given me this information, and told me that various stabilizing solutions are under test at the laboratories.

(3) Apparently the "stabilizer mixture" used for Toxin C has given satisfactory results, for Tables II and III indicate that the toxin has been potent up to two weeks after dilution, and later tests which we made show that six weeks after dilution this "stabilized Dick toxin" gave almost as good results as the fresh material. I understand from Dr. O'Brien that this result agrees with the laboratory investigations, and some made by other clinicians, and that his confident expectation is that this dilution is stable for much longer periods.

(4) The control Dick toxin must apparently be heated for four hours to make quite sure that the toxin is inactivated. With such a solution pseudo-reactions are extremely rare, but apparently one does encounter a patient now and then with what must be accepted as a pseudo-reaction, detectable only if frequent readings are made. Pseudo-reactors are so rare that one is almost safe in dispensing with the use of the control fluid when testing ordinary patients.

Summary

Different Dick toxins can be satisfactorily matched only if the technique is carefully standardized, frequent readings are made, and a considerable number of patients—probably fifty—are available.

A properly stabilized Dick toxin dilution apparently gives when six weeks old virtually as good reactions as when freshly made up.

Dick control fluid should be heated for at least four hours.

Pseudo-reactors are very rare, but are encountered from time to time.

I am indebted to Dr. J. McGarrity, medical superintendent of the hospital, for permission to carry out these tests and for his kindly advice and encouragement; and to Dr. R. A. O'Brien of the Wellcome Physiological Research Laboratories for supplying the materials used and for his helpful suggestions.

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FURTHER OBSERVATIONS ON THE TREATMENT OF TETANUS

BY

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A study of 229 cases of tetanus, with special reference to the antitoxin treatment, was recorded in a previous publication (1932). The following further observations are offered on the results of the treatment of 438 consecutive cases admitted to the J.J. Hospital from 1931 to 1935 inclusive.

Numerous papers have been published since 1932 in which the value of intrathecal injection of the antitoxin by cisternal puncture has been seriously questioned. The majority of workers advocate large doses intravenously in the early stage. Cole (1934) in a recent paper mentions that the incubation periods of our previous series were not given and that serious cases were excluded. It may be pointed out that the incubation periods of all cases were tabulated in the paper and the total mortality rate, including all serious cases, was given. The mortality rate, after deduction of cases resulting fatally within twenty-four hours of admission, was only a part of the tabulated results. The period of onset, which was not worked out in the previous series, has been included in the present one.

Recent work on the treatment of tetanus has proceeded mainly along two lines: the control of the exhausting spasms by the use of, among other things, curare and basal narcotics; secondly, the administration of a large initial intravenous dose of antitoxin. The following conclusions were reached in the previous paper:

1. That the use of tetanus antitoxin was rational and necessary.
2. The combined intrathecal (by the cisternal route), intravenous, intramuscular, and subcutaneous method gave the most promising results.

The present series of 438 cases was treated along similar lines. The antitoxin used, however, came from three different manufacturers, the potency marked on the tubes being uniform. The use of sedatives was standardized. Carbolic acid and magnesium sulphate injections were not used. Out of the total of 438 cases 209 (49.4 per cent.) were cured, 214 (50.6 per cent.) ended fatally, and 15 were discharged at request; 127 patients died within twenty-four hours of admission. Excluding these the mortality works out at 29.4 per cent. The corresponding figures for the previous series were 46.4 per cent. and 23.4 per cent. It may be mentioned that all the cases of the previous series had one brand of antitoxin.

For purposes of study the cases are grouped in the following tables: I.—Age. II.—Incubation period. III.—Period of onset. IV.—Period of onset with the incubation period. V.—Type of injury.

TABLE I.—Age

Age	1-10	11-20	21-30	31-40	Above 40	Not known
Number	78	89	120	101	44	6
Cured	42 (55.2%)	42 (49.4%)	63 (54.3%)	45 (46.4%)	15 (34.8%)	2 (40%)
Died	34 (44.8%)	43 (50%)	53 (45.7%)	53 (53.4%)	28 (65.2%)	3 (66%)

Discharged at request, 15.

This table corroborates the observation that the prognosis is better up to the age of 30 and then becomes progressively worse; very few patients over 50 recover.

TABLE II.—Incubation Period

Incubation period in days	1-5	6-10	Above 10	Not known
Number	73	78	100	172
Cured	27 (37%)	29 (37.1%)	68 (68%)	85 (49.4%)
Died	46 (63%)	49 (62.9%)	32 (32%)	87 (50.6%)

Discharged at request, 15.

Out of 214, 127 died within twenty-four hours; the incubation period of 58 out of 127 was under ten days, and in 52 it was not known, but was presumably short.

TABLE III.—Period of Onset

Days	1	2	3	4 and above	?
Number	108	85	94	96	55
Cured	44 (41.4%)	38 (45.2%)	47 (53.4%)	62 (68.1%)	18 (33.9%)
Died	63 (58.9%)	46 (54.8%)	41 (46.6%)	29 (31.9%)	35 (66.1%)
Died in 24 hours	40	25	25	16	21

Discharged at request, 15.

The previously published series did not contain this table. The rapidity of the development of symptoms appears to be the important factor in prognosis.

The following tables show the comparison between the incubation period and the period of onset.

TABLE IV.—Period of Onset with the Incubation Period

Incubation period	One Day				Two Days			
	1-5	6-10	11+	?	1-5	6-10	11+	?
Number ..	24	35	25	24	15	20	17	33
Cured ..	5 (20.8%)	12 (35.3%)	18 (72%)	9 (62.5%)	3 (20%)	8 (40%)	10 (62.5%)	17 (51.5%)
Died ..	19 (79.2%)	22 (64.7%)	7 (28%)	15 (58.9%)	12 (80%)	12 (60%)	6 (37.5%)	16 (48.5%)
Died in 24 hours ..	14	12	4	10	40	5	7	4

Incubation period	Three Days				Four Days and Above			
	1-5	6-10	11+	?	1-5	6-10	11+	?
Number ..	18	9	27	40	16	12	26	42
Cured ..	10 (58.8%)	2 (22.2%)	14 (55.5%)	21 (58.3%)	8 (50%)	7 (63.6%)	20 (80%)	27 (69.2%)
Died ..	7 (41.2%)	7 (77.8%)	12 (44.5%)	15 (41.7%)	8 (50%)	4 (36.4%)	5 (20%)	12 (30.8%)
Died in 24 hours ..	5	6	7	7	6	2	1	7

Discharged at request, 15.

No history was available with regard to the period of onset or the incubation period in fifty-five cases; out of these eighteen (33.9 per cent.) were cured and thirty-five died (66.1 per cent.). Twenty-one of these died within twenty-four hours; two were discharged at request.

The tables show that, even with a short incubation period, if the period of onset has been three days or over—that is, if the disease has been developing gradually and is not progressing rapidly—there are many chances of recovery.

TABLE V.—Type of Injury

	Nail	Septic	No Evidence of Injury
Number	65	248	115
Cured	23 (35.3%)	134 (51.77%)	52 (49.9%)
Died	42 (64.7%)	116 (48.3%)	56 (50.1%)

Discharged at request, 15.

The deep penetrating injuries, such as by nails, are more often followed by tetanus, and the cases carry a high mortality.

The type of case suitable for judging the results of any method of treatment falls within the groups of incubation periods from one to ten days and the period of onset from one to two days. If the mortality rate can be shown to improve in these groups by any method of treatment that method should receive serious consideration. In 115 cases no injury or source of entry could be discovered; this is a large proportion. Either apparently trivial or unnoticeable injuries may carry the infection, or the organisms that may be present in the lumen of the bowel may become pathogenic. Careful cultural examination of the stools of these patients as well as those of the community at large requires to be done if any light is to be thrown on this question of idiopathic tetanus. Even when there is no known portal of entry the disease takes a heavy toll, as fifty-six out of 115 cases showing no evidence of injury ended fatally.

Dosage and Mode of Administration

Great difference of opinion prevails among workers regarding the dosage and mode of administration of the antitoxin. Taylor (1934) thinks large doses unnecessary, while Miller and Rogers (1935) recommend large doses intravenously. Cole (1934) recommends one large dose intravenously and believes that the amount is sufficient to neutralize all toxin that may be present and that may be thrown into the circulation from the focus of infection. That some of the antitoxin is present in the blood ten days after administration Cole has proved by animal experiments.

In the present series moderately large doses have been used initially: 40,000 units intrathecally through the cisterna magna and 80,000 units intravenously and intramuscularly in equal parts. Daily administrations of 40,000 to 80,000 units according to the severity of the case, intravenously or intramuscularly, or both, were given till the spasms were fully controlled. It has been noted that premature stoppage of the serum has been followed by a return of the spasms. The total dose has often reached 400,000 units or more.

Experiments on Guinea-pigs

From recent experimental evidence it appears that intrathecal administration of serum does not act on any toxin present in the cerebro-spinal fluid, for none is found in it. We carried out certain experiments in guinea-pigs to find out if any toxin was present in the cerebro-spinal fluid. Serum and cerebro-spinal fluid from tetanus patients were injected intraperitoneally into guinea-pigs as well as serum from normal persons serving as controls; three guinea-pigs were used for each case in the beginning: 3 to 5 c.cm. of the serum and 5 to 10 c.cm. of the cerebro-spinal fluid were injected. The animals went into spasms from five to ten minutes after the injection of serum from the patients with tetanus, but did not develop any spasms after the injection of cerebro-spinal

fluid from tetanus patients or serum from the normal controls. This method can be used as a useful test for the diagnosis of tetanus in doubtful cases: 3 to 5 c.cm. of blood serum from the suspected patient are injected into the peritoneal cavity of a guinea-pig; the animal shows spasms, jerky movements of the head and body after a preliminary stiffness if the serum comes from a case of tetanus. An earlier diagnosis is thus possible in doubtful cases. The antitoxin in the cerebro-spinal fluid therefore acts through absorption in the blood stream. Clinically it controls the spasms better and earlier. This observation is made so often that it cannot be dismissed lightly. It is possible that the absorption is slower and steadier, and the effect of the intravenous injection is thus maintained for a longer period. The rate of absorption of the antitoxin from the cerebro-spinal fluid into the blood stream and the amount of antitoxin present in the blood from day to day after this injection are well worth study.

Sedatives to Control Spasms

The control of spasms by the use of suitable sedatives is the other problem before workers. A large number of sedatives are being advocated. The patient is in a state of hyperexcitability. All kinds of external stimuli throw him into spasms. The majority of these patients have received paraldehyde per rectum for the control of spasms—4 drachms in 2 oz. of saline by the drop method four-hourly, varied according to the requirements of each individual case. The use of somnifaine by injection or avertin per rectum has been advocated. Several articles have appeared on the use of curarine, the alkaloid from curare, the arrow poison. This has a paralysing action on the neuro-muscular junctions. The dose has to be carefully regulated, as respiratory muscles are likely to be paralysed if a large dose is inadvertently given. Very efficient nursing is therefore necessary if this drug is to be used as a routine measure. The work of Abel *et al.* (1934, 1935) may be mentioned here. They have overhauled the older conception of the disease and consider that the toxin has a peripheral action on the neuro-muscular junctions in the muscles themselves. The descending order of the spasms, however, has not been sufficiently explained.

Summary and Conclusions

1. A further series of 438 cases of tetanus has been observed, with special reference to the use of antitoxin.

2. The combined method of administration of the antitoxin, intrathecally through the cisterna magna, intravenously, and intramuscularly, has continued to be used in this as in the previous series.

3. The total mortality of all consecutive cases, except the fifteen that were discharged by request, has been 50.6 per cent., and after excluding those that died within twenty-four hours of admission, 29.4 per cent. This compares somewhat unfavourably with the previous figures, but may probably be explained by the fact that several brands of sera have had to be used in the present group while only one brand was used for the previously published group.

4. The routine use of paraldehyde per rectum is recommended in all cases as the most suitable sedative for hospital patients.

5. The clinical fact that the intrathecal administration of serum through the cisterna magna along with the other routes controls the course of the disease better, estab-

lishes the need for further study of concentration of antitoxin in the blood serum after intrathecal injections.

I take the opportunity of thanking Lieut.-Colonel Vazifdar, I.M.S., for facilities with regard to the treatment of the patients, and my successive house-physicians, without whose co-operation this work could not have been carried out. I also thank Dr. Manohar and Dr. Nene for helping me with the guinea-pig experiments.

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TREATMENT OF MENINGITIS WITH MENINGOCOCCAL ANTITOXIN

BY

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Until recent years the only specific agent available for the treatment of meningococcal meningitis was anti-meningococcal serum, but lately there has been produced a meningococcal antitoxic serum,* with which a series of four cases was successfully treated at the Kingston and District Hospital during the last year.

This serum is the result of the work of Dr. N. S. Ferry, who, with his associates, investigated the properties of broth filtrates of the meningococcus (1931), and showed that specific extracellular toxins were produced with each of the four Gordon types of the meningococcus. Further, it was found that animals could be immunized with each of the toxins and true antitoxins produced which, when investigated in the case of the guinea-pig and monkey (1932, 1934), rabbit (1934), and finally the human being (1935), were shown to have a curative effect against live virulent meningococci, besides a neutralizing one on the specific soluble toxins. These effects were not only specific for the type of meningococcus against which the antitoxin was produced, but were apparent to a lesser extent for all types of meningococci.

Dr. H. L. Hoyne (1935), in an investigation of a series of eighty-five cases treated with antitoxin, showed that the mortality was 23.5 per cent. as against 45.9 per cent. for cases treated with anti-meningococcal serum. After eliminating those cases in which the patient died within 48 hours of admission to hospital, the mortality was 9.6 and 29.6 per cent. respectively. Dr. Hoyne noted that following the use of antitoxin there was a prompt response of the infection, and he favoured large doses of 60 to 100 c.cm. administered intravenously in order that the toxin should be rapidly neutralized. It was recommended that these quantities should be given diluted in twice the volume of normal saline or 10 per cent. glucose solution.

The four cases reported below, all children, were treated with Ferry's serum on these lines, and gratifying improvement appeared to follow its use. In two cases meningococci were found in the cerebro-spinal fluid, but in the other two no organism was identified. In each case there was a rapid improvement in the general condition of the child associated with a decrease in the number of leucocytes in the cerebro-spinal fluid. The antitoxin was given

* By Parke, Davis and Company.