ference round the thigh than the other, the incisions were granulating in healthily, and the movements of the limb normal. On recent inquiry from his doctor it was learnt that the wounds soon healed, and the child has since remained perfectly well.

Remarks

On reviewing the literature on this subject I can find no statistics to show in what proportion of cases infection is confined to the subcutaneous tissues as above, but Choyce¹ mentions that it does occur. Thirty cases, however, have been reported of gas-gangrene infection following subcutaneous injections,^{2,3,4,5} either given hypodermically or as subcutaneous salines, but in the majority of these cases the infection became rapidly generalized and death ensued, or the patients recovered only after immediate multiple incisions and the administration of serum.

Perhaps Tissier's findings⁶ may explain the mildness of the infection. Tissier, in an article written in 1916, described experiments to show that gas-forming organisms in themselves had little power to cause gas gangrene, but when in association with other organisms they rapidly produced the typical disease. He showed that filtered cultures of *B. welchii* or *B. oedematiens* produced no effects; inoculation of animals with either of these organisms alone produced a hard oedema, which slowly disappeared, but when there was added to these cultures growths of aerobic bacteria the effects of malignant oedema were noted. He also stated that the presence of devitalized tissue was the necessary condition for the development of gas infection.

On looking at this boy's temperature chart it will be seen that the onset of severe symptoms coincided with the first appearance of pyogenic organisms in the pus. Up to this time on three occasions anaerobic organisms only were obtained from the wound, but on the twentieth day after infection the pus obtained on incision over the indurated area on the thigh gave a growth of haemolytic streptococci, and at this time the child's general condition was not so good. The hard, solid oedema of the leg, with absence of crepitus, suggested that the infection was mainly by organisms of the *B. oedematiens* type, although both groups of organisms were demonstrated in the pus.

It is also interesting to note in the cases quoted that the patients who received their infections by subcutaneous methods were in hospital suffering from some pre-existent disease or from loss of blood, and that other patients in better condition, who were given injections at the same time with the infected agent, did not develop gas gangrene.⁷ It seems strange in this case that, in the absence of devitalized tissue in a healthy child, gas gangrene should have developed at all, and it should be noted that at no time was there any evidence of infection extending beneath the deep fascia. How much of the child's good recovery was due to the early administration of serum or how much to the low pathogenicity of the organisms it is difficult to say.

In another case admitted to this hospital a few months ago, of severe compound fracture of the leg with much destruction of muscle, gas gangrene set in on the third day, although 12,000 units of anti-gas-gangrene serum had been given as a prophylactic dose on admission. It quickly subsided, however, following intravenous administration of large doses of

serum and free opening up of the wound. A reappearance of gas infection of the leg on the forty-fifth day after the injury followed encasement in plaster, but subsided again after serum injection and exposure of the wound to the air.

My thanks are due to Mr. Lewin for permission to publish this case, and to Dr. Knott of Guy's Hospital, who kindly confirmed the pathological findings.

IV = Intravenous. IM = Intramuscular. SC = Subcutaneous.

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INTERFERENCE IN THE SCHICK TEST BY DIPHTHERIA ANTITOXIN INJECTION IN THE HUMAN SUBJECT

BY

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The aim of this investigation was to find out how soon an injection of antidiphtheritic serum may be given to a suspected case of diphtheria after the performance of a Schick test without invalidating the result of that test.

Ker¹ (1924), in his presidential address to the Fever Hospital Group of the Society of Medical Officers of Health, gave an account of some work on this point. He assumed that all definite cases of diphtheria are Schick-positive at the onset of the disease, and, by testing such cases at varying intervals before the intramuscular injection of antidiphtheritic serum, he tried to find out how soon the serum had to be administered after the performance of the test in order to inhibit the positive reaction. He tested forty-seven cases two hours before the injection of serum, and of these forty-five yielded positive reactions and two were doubtful. Of nineteen cases tested one hour before the injection of serum, eighteen gave positive reactions and one a negative. The single patient reacting negatively died of circulatory failure within ten days after the test was performed, and it is possible that the circulation was already too depressed to respond to the stimulus of the test. Finally, fifty-six cases were tested immediately before the injection of serum, and of these forty-five had positive reactions, two were doubtful, and nine

were negative. He suggested various possible explanations as to why these nine cases reacted negatively. Two, for instance, were doubtful cases clinically, and in four there was some question as to the reliability of the test toxin. Nevertheless, nine out of fifty-six seems too high a proportion to be disregarded. Ker also reported results of seven Schick tests on cases of diphtheria immediately before the intravenous injection of antitoxin. Two of these reacted positively, four negatively, and one was doubtful.

Glenny and Hopkins² (1925) carried out similar tests on guinea-pigs. They found that the inhibition or reduction in size of a positive Schick reaction depended on the dose and the route of administration of a subsequent injection of antitoxin, and on the length of time that elapsed between the performance of the test and the administration of the antitoxin. For instance, a Schick reaction could be reduced to half its normal size either by giving 10 units of antitoxin intravenously thirty minutes, or 100 units intravenously ninety minutes, or 1,000 units intramuscularly forty-five minutes after making the test.

Nature of Investigation

In the present investigation it is assumed, as in Ker's work, that in the first few days of the disease all cases of diphtheria are potentially Schick-positive before receiving antitoxin. In making this assumption it is necessary to have strict standards by which to decide what is a case of diphtheria. The cases used for this work were a simple sample of those notified as diphtheria, and admitted to the North-Western Hospital, Hampstead, between November, 1932, and August, 1933; but only those which were undoubtedly diphtheritic from the clinical point of view, and which also yielded virulent cultures of *C. diphtheriae*, were considered to be proven cases of diphtheria.

Cases Receiving Intramuscular Serum

To begin with, only those patients who received all their antitoxin by the intramuscular route will be considered. Tests were performed as follows.

Group I.—Thirty-eight patients were Schick-tested immediately before an intramuscular injection of diphtheria antitoxin. Four of them were regarded as proven cases of diphtheria, and of these two gave positive and two negative reactions. Of the remaining thirty-four patients, fourteen yielded positive and twenty negative reactions.

Group II.—One hundred and fifty-one patients were each submitted to two Schick tests. In every case the first test took place one hour before, and the second immediately before, an intramuscular injection of antitoxin. Twenty-four patients were considered to be proven cases of diphtheria, and of these twenty-two reacted positively to both tests, and two were positive to the first but negative to the second. Of the remaining 127, eighty had positive reactions to both tests, fourteen were positive to the first and negative to the second, and thirty-three gave negative reactions to both tests.

Group III.—Three patients were each Schick-tested one hour before an intramuscular injection of antidiphtheritic serum. Two were looked upon as proven cases of diphtheria, and all three reacted positively.

Group IV.—Fifty-six patients were each submitted to two Schick tests. In every case the first test took place two hours before, and the second one hour before, an intramuscular injection of antitoxin. Sixteen patients were considered to be proven cases of diphtheria, and all of these gave positive results to both tests. Of the remaining forty cases, thirty-three were positive to both tests, one was positive to the first and negative to the second, and six were negative to both.

Table I shows the results of all Schick tests performed on patients who were regarded as proven cases of diphtheria, grouped according to the length of time the injection of antitoxin was delayed after each test. This

table is concerned with Schick tests and not with patients. If a patient is in, say, Groups II or IV, the results of his two tests are shown separately, each in its appointed row.

TABLE I

Time Elapsing between Schick Test and Intramuscular Injection of Antitoxin	Number of Tests Made	Result of Test		% +
		+	-	
0 hours	28	24	4	85.7
1 hour	42	42	0	100.0
2 hours	16	16	0	100.0

It is assumed that all the patients who formed the experimental material for Table I were potentially Schick-positive before receiving antitoxin. Four of the twenty-eight tests made immediately before the intramuscular injection of antitoxin were negative. Therefore a Schick test made immediately before such an injection of antitoxin does not give a reliable index of the patient's state of immunity at the time the test was performed. On the other hand, all of the forty-two reactions in the next row were positive. This, of course, is far from proving that all cases of diphtheria, if Schick-tested one hour before an intramuscular injection of serum, would show positive results to that test. First, these were all cases in which there was no doubt as to the diagnosis of diphtheria on clinical grounds alone. They therefore tended, on the whole, to be more severe than the average run of cases, and it is possible that they were, correspondingly, potentially more strongly Schick-positive than the average run of cases. Secondly, forty-two is a very small number from which to draw general conclusions. As might be expected, in the sixteen instances where the antitoxin was delayed for two hours after the test all the reactions were positive.

The reactions in Groups II and IV lend themselves to further consideration, because when a patient is submitted to two Schick tests the first, if positive, acts as a control on the second. Table II shows the results of the Schick reaction on all cases which were tested twice, and which reacted positively to the first test. This table is not confined to proven cases of diphtheria, but also includes those in which there was room for doubt about the diagnosis, and others which were not finally diagnosed as diphtheria at all.

TABLE II

Groups	Both Tests +	First Test + Second Test -	Total	% Positive to Both Tests
II	102	16	118	86.44
IV	49	1	50	98.00

Table II reveals that out of 118 patients in Group II who reacted positively to the test made one hour before the intramuscular injection of diphtheria antitoxin only 86.44 per cent. gave positive reactions to the test made immediately before they received antitoxin. Of the fifty patients in Group IV who reacted positively when the antitoxin was delayed two hours after the test, all but one also yielded positive reactions when the interval between test and injection of antitoxin was only one hour. The fact that one of these fifty had a negative reaction to the second test suggests that the interval of one hour between test and antitoxin is not long enough to ensure that the result of the test is unaffected by the injected antitoxin. This is supported by the observation that in some of the Group IV cases which reacted positively to both tests the reaction to the second was weaker than the reaction to the first. (It should be mentioned that,

for the sake of simplicity, doubtful reactions were recorded as negative.)

Considering Tables I and II together, there is no doubt that the Schick test performed one hour before an intramuscular injection of diphtheria antitoxin, though subject to some extent to the nullifying influence of the injected antitoxin, yet possesses a high degree of reliability. It is further suggested that the test carried out two hours before the intramuscular injection of antitoxin is more reliable still, and can be accepted for practical purposes as giving a true index of the patient's state of immunity at the time the test was performed.

Cases Receiving Intravenous Serum

Fourteen patients who were considered to be proven cases of diphtheria were each Schick-tested twice, the first test one hour before, and the second immediately before, an intravenous injection of antidiphtheritic serum. Their Schick reactions are shown in Table III.

TABLE III

Time Elapsing between Schick Test and Intravenous Injection of Diphtheria Antitoxin	Number of Tests Made	Result of Test		% +
		+	-	
0 hours	14	1	13	7.14
1 hour	14	10	4	71.43

A comparison between Tables I and III reveals that the proportion of positive reactions to the test immediately before intramuscular antitoxin is about twelve times as great as the corresponding proportion in the intravenous series. The results of the tests made one hour before giving antitoxin show a similar but less striking difference. Tables I and III, therefore, illustrate in human beings the same principles which Glenny and Hopkins established in guinea-pigs in connexion with the length of time the antitoxin was delayed after carrying out the Schick test and with the route by which the antitoxin was given. There was no evidence, in the cases used in this work, that the inhibition of a positive Schick reaction depended on the number of units of antitoxin given. There was not, however, very much variation in the size of dose employed, the number of "inhibited" reactions was small, and there was considerable variation in the age and weight of the patients.

Conclusions

1. It is suggested that two hours is a sufficient interval in which to delay an intramuscular injection of antidiphtheritic serum after making a Schick test in order to get a reliable result to that test.
2. It has been demonstrated that antidiphtheritic serum is much more efficient in inhibiting a positive Schick reaction when introduced by the intravenous route than by the intramuscular.

I wish to express my thanks to Dr. A. Joe, medical superintendent of the North-Western Hospital, Hampstead, for suggesting the subject of this work, and for much helpful advice.

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The verbatim report of the twentieth annual conference of the National Association for the Prevention of Tuberculosis, held in London in June, 1934, is now published, and copies (7s. 6d., post free) may be obtained on application to the Association at Tavistock House North, Tavistock Square, London, W.C.1.

A CASE OF EVIPAN PARALYSIS

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The following case is one of widespread paralysis following the use of evipan for general anaesthesia with no pre-medication, and as we can find no similar case in the literature we think it may be worth recording.

A Chinese patient, aged 29, was admitted to the Johore Bahru General Hospital on February 5th, 1934, complaining of swelling, redness, and pain in the region of the left knee-joint of four days' duration. The surface appearance suggested a cellulocutaneous erysipelas. On February 8th operation was decided upon, and performed under evipan anaesthesia. The one gram of evipan in the usual stock ampoule was dissolved in the 10.5 c.cm. of distilled water in the other stock ampoule. Nine c.cm. of this solution was given intravenously at 11 a.m. very slowly, stopping for a few seconds after every 1/2 c.cm. and taking six minutes to introduce the total 9 c.cm. The patient began to yawn after 2 1/2 c.cm., and to snore after 4 c.cm. The operation was started at 11.10 a.m. and lasted seventeen minutes. An incision five inches long was made on the outer side of the left thigh, and a large abscess cavity was opened, evacuated of all pus, and irrigated; the abscess was found not to communicate with the knee-joint.

After the operation the patient was breathing normally and moving his eyeballs, but he did not recover full consciousness till 10.30 o'clock that night. During this long interval he made movements of the eyes, face, and limbs, and swallowing movements. His pulse was rapid (140), but had been nearly as fast before operation (134). An injection of strychnine 1/30 grain was given at 3 p.m. that day, and oxygen was then administered for half an hour because he was so long unconscious; coramine, as recommended by the manufacturers, was not available. At 10.30 p.m. he at last began to answer questions, and warm drinks were given. He was fully conscious next morning.

It was not until February 17th that the assistant surgeon in charge of the case noticed there was severe paralysis. The patient had in the meantime been gravely ill owing to his septic condition, and had not himself called attention to his paralysis; when questioned, he stated that it had been gradually coming on since the date of his operation, but had not been present before. On detailed examination there was flaccid paralysis of the trunk, so that the patient could not move himself in bed, of both lower limbs, and of the distal portion of the upper limbs. There was bilateral ankle-drop and wrist-drop. The knee-jerks, ankle-jerks, and biceps-jerks were absent; the plantar responses were flexor, and abdominal cutaneous reflexes present. There was no loss of control of the sphincters. Sensibility to touch and pain was diminished below the knees, but not affected in the upper limbs. Kahn test of the blood and of the cerebro-spinal fluid was negative.

General wasting of many muscles followed, with consequent loss of weight; by April the weight was down to 89 lb., but, unfortunately, it had not been taken earlier. On June 23rd, when recovery was almost complete, it was 100 lb. The septic condition of the leg gradually cleared up, although for several days after the operation it was spreading; the wound was healed by the middle of April, and all inflammation had then disappeared. There had been considerable pyrexia before the operation, but there was none after, except a temperature of 100° F. on the day following and a rise to a 100° on March 9th and 10th, which yielded at once to quinine. High fever occurred on April 22nd, with painful enlarged spleen and the appearance of blood and mucus in the stools; this subsided with quinine treatment in a week, and was probably malarial, though no parasites were found in the blood; there were no causative organisms in the stools.

For the paralysis the patient received massage, rhythmically interrupted sinusoidal current, and a general tonic of iron and strychnine; flexion and extension of wrists and feet