A STUDY OF PASSIVE IMMUNISATION IN SCARLET FEVER.

BY ALEXANDER JOE, D.S.C., M.D. EDIN.,
MEDICAL SUPERINTENDENT, NORTH-WESTERN HOSPITAL, LONDON;
AND
R. SWYER, M.R.C.S. ENG., D.P.H.,
SENIOR ASSISTANT MEDICAL OFFICER TO THE HOSPITAL.

ANY procedure which will cut short an outbreak of infectious disease must be regarded from all points of view as of very great value. Its value to the contact cannot be over-estimated, for by its means he may escape an attack of the disease and the consequent possible risk to life and well-being, certain loss of time, and in many cases financial loss. Also it is obvious that when the outbreak occurs in hospital and when quarantine has to be observed a certain proportion of the contacts are bound to be detained for a longer or shorter period after they are fit to return home. Should a secondary case arise this period must, of course, be lengthened by another quarantine period and, considering the problem from the standpoint of hospital administration, any method of obviating or reducing quarantine periods must result in a considerable saving of patients' accommodation and expense. In a clinical investigation of the new work on scarlet fever [1] one of us demonstrated that a passive immunity to scarlet fever could be brought about by the injection of scarlet fever antitoxic serum, and it was to make a detailed study of this phenomenon and to test its practical possibilities in the limitation of outbreaks of scarlet fever in the non-scarlet fever wards of an infectious diseases hospital that the following work was carried out. Our study has extended over a period of two years; observations have been made in 40 separate outbreaks of scarlet fever and include the immunisation records of over 250 individuals. Other workers have employed the method, particularly in children's [2] and infectious hospitals [3 4 5 6] throughout the country, and it appears to have been successful both when the immunity was estimated by the Dick test and when it was assessed in terms of actual resistance to the disease.[4 7] The dosage now generally recommended is from 2·5 to 5 c.cm. of the concentrated antiserum, but, as James [8] has pointed out, comparatively little work has been published in this country on the amount of antitoxin necessary to secure protection. As a result of his investigation he came to the conclusion that 5 c.cm. is usually sufficient to protect susceptible contacts for a minimum period of seven days, but that certain highly susceptible individuals giving a strongly positive Dick reaction probably required 10 c.cm. Cruickshank [9] has also worked at this problem and states that in general 2·5 c.cm. of a concentrated antitoxin protects for three to six days, 5 c.cm. for seven to ten days, and 10 c.cm. for two or three weeks, and in another paper [10] he indicates that the immediate protection afforded by different doses of the antitoxin does not vary very much, but that the chief effect of increasing the dose is to bring about a more lasting immunity.

Methods.

On the occurrence of a case of scarlet fever in a non-scarlet ward the cross-infected case was promptly isolated and search made for a probable infecting case. One of two measures was then adopted, attempts being made to limit the outbreak either by quarantining the ward or by protecting the exposed susceptibles, after which quarantine was removed. As far as possible these measures were used alternately, so that the results of the passive immunity experiments were controlled by those in which quarantine was observed. Since all the wards in which scarlet fever appeared contained an average number of 20 beds, the total numbers exposed would be comparable. In the passive immunity experiments all contacts were Dick-tested immediately, the results being scrutinised after 24 hours and classified as follows: Reactions under 10 mm. in diameter Class I., from 10–20 mm. Class II., from 20–30 mm. Class III., and above 30 mm. Class IV. Following the practice of other observers, we have for practical purposes regarded Class I. reactors as immune. The susceptibles were then given their injections of scarlet fever antitoxin by the subcutaneous or intramuscular route, and were re-tested at an interval of 24 or 48 hours and at weekly intervals until they became positive again or were discharged from hospital. The toxin used in the testing was supplied by Dr. Hartley, of the Medical Research Institute. We were conversant with its properties and we have proved it over a long series of comparative tests to be exactly comparable with the Dick reagent used extensively in this country. The antitoxin was the ordinary commercial preparation put on the market by two well-known firms.

Immediate Results of Various Doses of Antitoxin.

In an attempt to decide upon the optimum dosage sufficient for immediate and complete protection we have employed injections of 3 c.cm. in 57 cases, 4 c.cm. in 41 cases, 5 c.cm. in 120 cases, and 10 c.cm. in 43 cases. On re-testing we found that after a 3 c.cm. dose 51 individuals (89·4 per cent.) became Dick-negative; after 4 c.cm. 40 (97·5 per cent.) became Dick-negative; after 5 c.cm. 101 (84·1 per cent.) became Dick-negative; and after 10 c.cm. 41 (95·3 per cent.) became Dick-negative.

These results raise some very interesting practical questions. For instance, it is a matter of considerable importance to find in a significant series of cases that 5 c.cm., which has come to be widely recommended as a suitable dose for the purpose, fails to confer passive immunity in 16 per cent. of cases, and that even by doubling this dose we cannot be sure of conferring a passive immunity on every case. It is also interesting to find that 3 c.cm. and 4 c.cm. doses seem to be as effective as the larger amounts. In considering these results as a whole, three factors occur to us as requiring attention. These are the possible variation of antitoxic content of various batches of serum, the question of age, and the state of susceptibility of the patient. Examination of the individual results in the various groups of patients immunised at any single time shows that no great variation in antitoxic content in the various batches could be detected. The 5 c.cm. series, the largest, was composed of 11 groups, each consisting of from 8 to 15 susceptibles. Only in three of these did we obtain a complete group immunity after protection, whereas in the remainder, according to the smaller or larger numbers comprised in the group, there were one, two, or three failures, and in no experiment were the unsuccessful cases concentrated in any single group. The same fact emerges from an analysis of group results in the other series. The question of age has also been examined; in the 5 c.cm. group there were seven failures to protect among 57 children under the age of 5, or 12·2 per cent. In the age-group 5–10, consisting of 47 children, there were 13 failures, or 27·6 per cent., and in the age-group 10–15 there were 5 failures out of 12, or 41·6 per cent. In spite of the fact that this important point is not brought out in either of the series immunised with 3 c.cm. or 4 c.cm.—all the failures in these being scattered indiscriminately throughout the age-periods under 5—we are inclined to attach importance to the suggestion implied in the analysis of the larger numbers, and feel that in considering dosage regard should be paid to age. The question of susceptibility also requires attention, and we have been able by grading our reactions to correlate this factor with the results of passive immunisation. In the 5 c.cm. series we find that this dose failed in 7 out of 16 Class IV. reactors (43·7 per cent.), in 9 out of 52 Class III. reactors (17·3 per cent.), and in 7 out of 52 Class II. reactors (13·4 per cent.). Unfortunately the Dick reactions were not graded in the 4 c.cm. series, but most of the 3 c.cm. series and all of the 10 c.cm. were graded, and an analysis of these brings out the same point. Our failures may partially be ascribed, therefore, to the high susceptibility, as shown by the Dick test, of a proportion of the patients. From a study of our records we find that after intramuscular inoculation of the protective dose 6 per cent., and after subcutaneous injection 11 per cent. of positive

Dick re-tests at a 24-hours' interval subsequently became negative, whereas after a 48-hour re-test further change in the reaction was unlikely. We are therefore inclined to recommend the intramuscular route to secure as rapid absorption as possible, and that a 48-hour interval be observed before re-testing to estimate the effect of immunisation.

Duration of Passive Immunity.

This is a matter of some importance and, on the analogy of other infections in which it is possible to produce this type of protection, we should not expect it to be of long duration. It is generally considered that, to be of value, passive immunity in scarlet fever should at least endure beyond the limit of the incubation period—i.e., for 7–10 days. On consulting the table it can be seen how far that demand is satisfied by different doses. For various reasons we were not able to follow up all our cases until they returned to their original positive reaction, but in each series of cases we think we have been able to follow up a sufficient number as far as the end of the second week to supply a satisfactory figure on which to calculate the probable number of negatives if all had been re-tested, and thereby establish a percentage in which the probable error is not great. Again the results vary with such irregularity that it is difficult to draw conclusions. We find that at the end of the first week, after a 3 c.cm. dose 75·4 per cent., and after a 4 c.cm. dose 92·6 per cent. are still negative, but after a 5 c.cm. dose only a little over half, 56·6 per cent., have not relapsed to the state of susceptibility. At the end of the second week there is a further falling off

Table showing Incidence and Duration of Passive Immunity after Various Doses of Scarlet Fever Antitoxin.

Dose: c.cm.	Date of re-test.	Total.	Pos.	Neg.	Negs. not re-tested.	Prob. neg.*	Per cent.
3	1–2 days	57	6	51	—	—	89·4
	1st week	39	6	33	12	43	75·4
	2nd „	24	9	15	9	27	47·3
	3rd „	12	3	9	3	—	—
	4th „	7	3	4	2	—	—
	5th „	4	0	4	—	—	—
4	1–2 days	41	1	40	—	—	97·5
	1st week	39	2	37	1	38	92·6
	2nd „	32	12	20	5	24	58·5
	3rd „	5	2	3	15	—	—
	4th „	2	2	0	1	—	—
5	1–2 days	120	19	101	—	—	84·1
	1st week	95	31	64	6	68	56·6
	2nd „	51	16	35	13	47	39·1
	3rd „	29	13	16	6	—	—
	4th „	10	4	6	6	—	—
10	1–2 days	43	2	41	—	—	95·3
	1st week	36	1	35	5	40	93·0
	2nd „	28	3	25	7	36	83·7
	3rd „	21	8	13	4	—	—
	4th „	6	0	6	7	—	—

* Prob. neg. = Probable number of negatives if all surviving negatives from previous re-test had again been re-tested.

in the numbers, the 3 c.cm. and 4 c.cm. series now showing 47·3 and 58·5 per cent. respectively of negatives, whilst the 5 c.cm. series give a smaller percentage still—viz., 39·1. Again, the 10 c.cm. results are the most satisfactory since, although the percentage of negative results immediately after immunisation is not so high as obtained with the 4 c.cm. dosage, 93·0 and 83·7 per cent. of negatives at the end of the first and second weeks respectively may be regarded as satisfactory. This result also confirms the observation of Cruickshank that increasing the dosage for passive immunity in scarlet fever tends rather to prolong the duration of protection than to give a great increase in the number of negative reactions. It may be fair to attribute the better results obtained in the 3 c.cm. and 4 c.cm. series, when compared with the 5 c.cm. series, to the smaller total numbers involved, and if we do so, then we must regard the 10 c.cm. series as the only satisfactory one from the point of view of persistence.

During the course of the investigation eight cases previously passively immunised subsequently developed scarlet fever, and, since these have a direct bearing on the protective value of the process and also on the duration of the immunity, details are appended :—

CASE 1, aged 5. Exposed on Feb. 9th, 1928, and found Dick-positive. On the 10th given 5 c.cm. antitoxin. On the 12th was still Dick-positive and developed scarlet fever on that date—i.e., two days after immunising injection.

CASE 2, aged 6. Exposed Feb. 6th, 1928, and found Dick-positive. On the 10th given 5 c.cm. antitoxin. On the 12th was Dick-negative and developed scarlet fever on that date—i.e., two days after immunising injection.

CASE 3, aged 10. On Oct. 27th, 1927, was Dick-positive. Exposed Nov. 16th. On the 17th given 5 c.cm. antitoxin. On the 18th was Dick-positive and on Nov. 21st took scarlet fever—i.e., four days after immunising injection.

CASE 4, aged 15. Exposed Dec. 13th, 1926, and found Dick-positive. On the 14th 3 c.cm. antitoxin. On the 15th and 21st was Dick-negative. On the 24th was Dick-positive and took scarlet fever—i.e., ten days after immunising injection.

CASE 5, aged 3. On March 24th, 1927, was Dick-positive. Exposed April 14th. On the 15th given 4 c.cm. antitoxin. Was Dick-negative on the 16th and 21st, but Dick-positive on the 28th. On May 3rd took scarlet fever—i.e., 19 days after immunising dose.

CASE 6, aged 8. On July 20th, 1927, was Dick-positive. Exposed on the 22nd. On the 23rd given 5 c.cm. antitoxin. August 1st was Dick-negative, but found Dick-positive on the 8th. On the 12th took scarlet fever—i.e., 20 days after immunising dose.

CASE 7, aged 2. Exposed April 15th, 1928, and found Dick-positive. On the 16th given 5 c.cm. antitoxin. On the 18th was Dick-negative, but on the 25th and May 2nd was Dick-positive. On the 9th took scarlet fever—i.e., 23 days after immunising dose.

CASE 8, aged 7. On Oct. 27th, 1927, was Dick-positive. Exposed on Nov. 16th. On the 17th given 5 c.cm. antitoxin. On the 18th was Dick-negative, but on the 25th and Dec. 2nd was Dick-positive. On the 15th took scarlet fever—i.e., 28 days after immunising dose.

It is interesting to note from these cases that in all except the second the presence or absence of immunity was correctly indicated by the Dick test. It is difficult to explain Case 2, except on the ground that it probably falls into the varying percentage of cases of scarlet fever which practically all workers have found to be Dick-negative even in the earliest stages of the disease. We suggest that the first three cases were incubating scarlet fever at the time of immunisation, and that the protective injection of 5 c.cm. of antitoxin did not succeed in blocking the onset and apparently failed to have much effect in modifying the incubation period, assuming that all three were the direct consequence of their respective primary infecting cases. All cases, however, were mild and without complications. Whatever the explanation, their occurrence seems to point to the necessity for a serum which in reasonably small doses will confer a more certain immunity. The remainder of the cases serve to emphasise the fact that, while passive immunisation may carry the susceptible contact over the immediate dangers of an exposure, it is transient and fails to protect against subsequent exposures at as short a space of time as three or four weeks after the first.

Comparison of Quarantine and Immunisation Methods.

In 21 of the 40 outbreaks studied the usual methods of quarantine for ten days were carried out. Of these 11 ended without further cases developing within the quarantine period, but in ten instances secondary cases appeared, resulting in the infection of 13 individuals. In the 19 outbreaks dealt with by passive immunisation 17 were free from the occurrence of subsequent cases within ten days of the appearance of the primary case. In two outbreaks, however, secondary cases did appear. These numbered three, one outbreak being responsible for Cases 1 and 2 detailed above, and another for Case 3. These figures give a clear indication of the protective value of passive immunisation and constitute a strong argument

in its favour. Perhaps less important than the actual prevention of cases of scarlet fever, but nevertheless of considerable moment to those responsible for hospital administration, is the saving in accommodation. By reducing the period of quarantine from ten to three days, the time occupied by testing and immunising, there was a clear saving of seven days in each of 19 outbreaks, or a total of 133 days—i.e., roughly four and a half months in two years. If the quarantined outbreaks had been immunised as well we should have been able to double that gain, so that the equivalent accommodation of one ward for four and a half months in one year would have been set free.

Serum Reactions.

Since the majority of our scarlet fever cross-infections occurred amongst diphtheria patients who had been sensitised to horse serum, it was inevitable that there should be a fairly heavy incidence of serum reactions. For the same reason it was often quite impossible to determine whether to attribute any given rash to the therapeutic diphtheria antitoxin or the scarlet fever prophylactic, and we cannot offer any statistical evidence on this point. When patients had received diphtheria antitoxin more than ten days previously they were desensitised by an injection of 0·5 c.cm. of normal horse serum. Serum sickness was confined to local reactions and generalised urticarial rashes, and, while inconvenient, the symptoms were transient and no serious effects were produced.

Discussion.

This phase of development of the recent work on scarlet fever has not by any means reached finality. We had hoped to be able to outline a plan which could be adapted to any outbreak and which, involving no more trouble than a preliminary Dick test followed by the immunising dose, could be relied upon to give a solid immunity of a reasonable duration. Experiment has shown that the problem of passively immunising the susceptibles in an exposed ward-population cannot yet be reduced to these terms, and it seems to us that the chief part of the difficulty is due to the fact that we are working with a relatively weak antibody. This is apart from the handicap imposed by the fact that no method of standardisation has yet been evolved which can provide us with an exact measure of the antitoxic content. In spite of these limitations we think the case for passive immunisation is strong. It is true that the present type of scarlet fever is mild, but in the past we have seen death resulting from scarlet fever complicating other acute infections and also such operations as that for cleft palate. If we add the administrative advantages in the saving of hospital accommodation, and economic advantages to adult patients in the avoidance of loss of working-time, we consider that this procedure provides an opportunity which no one can afford to dismiss.

The results in attempts to limit outbreaks of scarlet ever by passive immunisation are encouraging, but complete efficiency requires the introduction of an antiserum comparable in potency with that of diphtheria antitoxin. At present we suggest that susceptible contacts up to the age of ten years giving a Dick reaction of less than 30 mm. diameter should receive 5 c.cm. antitoxin intramuscularly and should be Dick-tested again after 48 hours, the dose to be repeated in positive reactors. Contacts over 10 years of age and those of any age giving a reaction of 30 mm. or over should receive an initial dose of 10 c.cm.

Bibliography.

1. Joe, A.: THE LANCET, 1925, ii., 1321.
2. McClean, D.: THE LANCET, 1927, i., 483.
3. Kinloch, J. P., Smith, J., and Taylor, J. S.: Jour. of Hyg., 1927, xxvi., 327.
4. Harries, E. H. R., Hervey, D., and Fellowes, V.: Brit. Med. Jour., 1926, i., 864.
5. Benson, W. T.: Jour. Roy. San. Inst., 1928, xlix., 108.
6. O'Brien, R. A.: Brit. Med. Jour., 1928, ii., 434.
7. Harries, E. H. R.: Med. Officer, 1927, xxxviii., 153.
8. James, E.: THE LANCET, 1928, i., 227.
9. Cruickshank, R.: Glasg. Med. Jour., 1928, cix., 46.
10. Same author: THE LANCET, 1928, ii., 274.

OBSERVATIONS ON THE
SEDIMENTATION RATE IN PULMONARY TUBERCULOSIS.

BY R. R. TRAIL, M.D. ABERD., M.R.C.P. LOND.,
MEDICAL SUPERINTENDENT, KING EDWARD VII. SANATORIUM, MIDHURST;
AND
DORIS M. STONE, M.D., D.P.H. LOND.,
PATHOLOGIST TO THE SANATORIUM.

IN November, 1926, we began an investigation to determine the value of the sedimentation rate in the diagnosis and prognosis of pulmonary tuberculosis. The method adopted was that used by the late Dr. Arthur Inman, of Brompton Hospital, which differs from the usual methods in that very small amounts of blood are taken, permitting frequent examinations over long periods. Various methods of treatment were thus investigated—ordinary sanatorium routine, artificial pneumothorax, and sanocrysin.

Technique.

To two volumes of a sterile solution of 3·8 per cent. sodium citrate eight volumes of blood are added. The unit of volume is one drop of blood from a broad-ended glass pipette; the blood is drawn from an ear or finger and mixed in a watch-glass. A column of the diluted blood, 4 inches (=100 mm.) long, is drawn by capillary attraction into a fine glass tube about 6 inches long and of 2 mm. bore. The tube is sealed with sealing wax and placed vertically in a bed of plasticine. In this investigation the length of the clear fluid column above the sedimented red cells was measured at the end of an hour, in millimetres, this giving the result directly as a percentage. Any reading above 6 mm. for a man and 12 mm. for a woman is considered abnormal. In cases investigated over a long period the results were plotted in graph form (Fig. 1).

All cases entering the sanatorium were investigated a week after admission and at monthly intervals until discharged. Cases undergoing pneumothorax treatment were investigated once a week for the first month and afterwards every fortnight.

The Test in Diagnosis.

It has been proved by many investigators that the sedimentation test has little value in diagnosis and this agrees entirely with our findings. Of the 360 cases who entered the sanatorium during the period covered by the investigation 318 were clinically tuberculous, while in the remaining 42 no positive evidence was obtained. In these patients the changes in the sedimentation rate were as follows:—

A. *Clinically Tuberculous Cases.*

Sputum.	Sed. rate. Normal.	Sed. rate. Increased.	Total.
T.B.+ ..	3	230	233
T.B.— ..	6	79	85
All cases	9	309	318

B. *Clinically Non-tuberculous Cases.*

—	Sed. rate. Normal.	Sed. rate. Increased.	Total.
Nil found ..	18	3	21
Other chest conditions..	8	7	15
Non-pulmonary conditions..	3	3	6
All cases ..	29	13	42

Thus, of 318 clinically tuberculous cases, 309, or 97 per cent., gave an increased sedimentation rate, while 9, or 3 per cent., gave a normal figure. Of the 42 clinically non-tuberculous cases, 29, or 69 per cent., gave a normal figure, while in 13, or 31 per cent., the rate was raised. These results indicate that, while an increased sedimentation rate may be used in conjunction with clinical findings to assist in the diagnosis of pulmonary tuberculosis, yet its usefulness in this respect is more than modified by the fact that other