THE SCHICK REACTION:

A CLINICAL TEST FOR THE DETERMINATION OF
SUSCEPTIBILITY TO DIPHTHERIA.

BY

GLADYS WARD, M.D., D.P.H. EDIN.,

ASSISTANT MEDICAL AND CHILD WELFARE OFFICER, DEPTFORD.

Preparation of the Toxin and Technique of the Injection.

For purposes of the Schick test¹ a toxin which has been ripened for at least a year, and then carefully standardized by determining the minimal lethal dose for a 250-gram guinea-pig, should be used. The bulk toxin will keep its strength very well if a ripened toxin is used. A dilution of the toxin is then made, of such strength that 1 c.cm. contains one-tenth of a minimal lethal dose. The amount actually injected in the test is 0.2 c.cm. of this dilution—that is, one-fiftieth of a minimal lethal dose.

To make the injection it is essential to have a short, sharp-bevelled needle which fits accurately on the syringe. A 1 c.cm. Record syringe is found most convenient. The flexor aspect of the right forearm just below the bend of the elbow is the selected spot. The arm having been first cleaned with ether or spirit, the skin is made taut between the forefinger and thumb of the left hand, and 1/5 c.cm. of the diluted toxin is injected intracutaneously. The result is absolutely useless if the injection be made subcutaneously. When done correctly a raised white wheal with a definite edge, and on which the pores of the skin are visible, is produced. Finally, if the test has been successfully performed, it should be possible to express a small drop of blood-stained serum from the site of the injection.

A true positive reaction is clearly visible at the end of twenty-four hours as a clearly circumscribed red area, generally about 3/4 inch in diameter, and accompanied by slight infiltration. This increases in intensity for the next three or four days, and then gradually fades, leaving a still distinct area of pigmentation and scaling. This pigmentation is generally faintly visible at the end of four or five weeks, and thereafter disappears. There is no general reaction. People who are using their arms a great deal may complain of some stiffness and local irritation.

A pseudo-reaction appears earlier, reaching its height in from twenty-four to thirty-six hours. It is not definitely circumscribed, and often shows a secondary areola, which fades off into the surrounding skin. The reaction begins to fade at the end of thirty-six hours, and has generally quite disappeared at the end of seventy-six hours, leaving no scaling; but, occasionally, a faint bluish mark persists on the skin for some days. The patient complains more frequently of stiffness and soreness of the arm, and in one or two cases a general reaction (headache, vomiting, etc.) has been noted.

A reaction is said to be negative when there is absolutely nothing to be seen at the site of the injection at any time.

The majority of the readings referred to in this paper were made at twenty-four hour, seventy-six hour, and seven-day intervals, the reasons for these intervals being as follows:

(a) At the end of twenty-four hours both the true and the pseudo-reaction, should it be present, are well marked.

(b) The pseudo-reaction has begun to fade at the end of forty-eight hours, and by the time seventy-six hours have elapsed has generally completely disappeared, thus rendering the second reading much simpler.

(c) The third reading was taken at the end of a week or ten days. I consider the latter quite reliable, and more convenient when dealing with patients in a general hospital.

The reading of the different reactions, after a short apprenticeship, presents little difficulty, except in cases complicated by a pseudo-element, and in these cases a "control" test may be done at a site on the left arm corresponding to the original test on the right. The control toxin is heated to 75° C. for ten minutes, whereby the specific toxin is destroyed, and the proteins, to which the pseudo-reaction is due, are left unchanged.

Careful records should be kept—these to include the name, age, and address of the patient, the date of injection, subsequent readings, and final remarks and results of each case.

It is, of course, essential that the toxin be reliable. I was fortunate in obtaining from Dr. Claude B. Ker one which had been prepared by Dr. R. A. O'Brien, and which had been proved to be entirely satisfactory.

The test depends on a local irritant action of minute quantities of diphtheria toxin given intracutaneously. A negative reaction indicates that the individual is possessed of a necessary number of antibodies to neutralize the

toxin, and is therefore immune to the disease at the time when the test is made. According to Schick himself a negative reaction indicates at least 1/30th of a unit of antitoxin per cubic centimetre of blood—that is, sufficient to protect against diphtheria. Von Behring maintains that 1/100th unit is sufficient. A positive reaction indicates that the individual tested does not contain sufficient antitoxin in his blood to render him immune. A pseudo-reaction is probably a local sensitization phenomenon of a protean character, since a similar reaction can be produced with toxin heated to 75° C. for five minutes, or with dilutions of the autolyzed substance of the diphtheria bacillus in which no toxin is present.

Influence of Age on the Schick Reaction.

The following table has been compiled from tests done in the Royal Hospital for Sick Children and in Craiglockhart Poorhouse Hospital, Edinburgh.

Age.	Number.	Negative.	Positive.	Percentage Positive.
0 to 6 months	25	23	2	8
6 months to 2 years ...	41	21	20	50
2 to 5 years	26	10	16	61
5 to 10 years	44	30	14	34
10 to 15 years	14	10	4	28
Total	150	94	56	37

Here we find that the greatest number of positive Schick reactions occurred in children between the ages of 6 months and 5 years. This we know to correspond with the age incidence of diphtheria.

The following is a table showing the number of deaths from diphtheria in this country in 1917.

All Ages.	- 1	1 -	5 -	10 -	15 -	25 -	35 -	45 -
648	42	404	145	33	6	7	3	8

From this we see that no less than 63 per cent. of the total number of deaths occurred between the ages of 1 and 5 years, and it is interesting to compare this figure with that quoted in the previous table of children between the ages of 2 and 5 years who give positive Schick reactions, the percentage of these being 61.

Influence of Concurrent Disease on the Reaction.

The following table gives the results in the scarlet fever wards:

Age.	Number.	Negative.	Positive.	Percentage Positive.
0 to 1 year	0	0	0	0
1 to 2 years	2	0	2	100
2 to 5 "	17	0	17	100
5 to 10 "	47	21	26	55.3
10 to 15 "	30	11	19	63
15 years and over ...	54	34	20	37
Total	150	66	84	56

These results, though comprising too small a number to be of great value, correspond fairly closely with those published by Dr. Leete² last year, his total percentage of positive results being 57.2.

Comparing the results between children tested in the scarlet fever wards and in the wards of a general hospital we find in the former 66 per cent. positive between the ages of 6 months and 15 years, in the latter only 37 per cent. For a long time, moreover, it has been a recognized fact that, in spite of all precautions, cases of diphtheria occur in the scarlet fever wards more readily than in others. Zingher³ suggests that there may be a destruction of the natural diphtheria antitoxin during an attack of

scarlet fever, while Von Behring has suggested that there is a temporary loss of natural immunity to diphtheria during the acute febrile stage of the disease.

Among the cases studied at the Sick Children's Hospital the actual disease from which the child was suffering at the time did not appear to have any definite bearing on the reaction, but the "acuteness" or "chronicity" of the case apparently bore a close relationship. The percentage of positive Schick reactions is given under the following headings:

Respiratory diseases (not tuberculous), 56.25 per cent. Alimentary diseases (not tuberculous) 50 per cent. Tuberculosis 45.5 per cent. Nervous disorders 33.5 per cent. Rheumatism 27 per cent. Rickets 16.6 per cent. Diseases of kidney and bladder 16.6 per cent. Congenital syphilis 14 per cent.

Another series of cases was then taken and divided into two groups—acute and chronic—care being taken to exclude entirely all such cases as could not be definitely classified.

The "chronic" cases included chronic tuberculous infections, long-standing empyemas, congenital syphilis, etc., while the "acute" were chiefly made up of pneumonia, acute bronchitis, acute gastro-enteritis, etc. The results were as follows:

Of chronic cases 28 per cent. were positive.
Of acute cases 60 per cent. were positive.

We see, therefore, that the number of positive Schick reactions found in the acute cases was as high as that found among scarlet fever patients. The figures obtained by Dr. Leete, in the 500 scarlet fever cases tested by him in the Edinburgh City Fever Hospital, show that between the ages of 1 and 15 years 60 per cent. were positive; my own figure is somewhat higher—namely, 67 per cent. "Acute general cases" in the same age group also gave 60 per cent. positive Schick reactions.

It was interesting to note, moreover, in several cases of *tabes mesenterica* tested, that most of those who came in almost in *extremis* and were "hopeless" from the first gave a strongly positive reaction, whilst those who were less severely infected and left hospital "improved" gave a negative reaction. Another interesting example was supplied by two sisters who were in the ward at the same time suffering from dysentery.

One was aged 7, the other 8, and neither of them had diphtheria. The infection in both cases was by the Shiga bacillus. The younger, who was the more severely ill on admission and subsequently died, gave a strongly positive reaction, whilst the elder, who was only mildly infected and made a good recovery, gave a negative reaction.

It has been noted by various observers that immunity or non-immunity to diphtheria runs in families. Is not this case, then, very suggestive of the fact that any acute infection may cause a temporary loss of natural immunity, and that the high percentage of diphtheria cases occurring in scarlet fever wards may also be explained on these grounds?

It has been suggested that the Schick reaction might be due to a general reaction on the child's part to any toxic material. Dr. Ellsworth Moody⁴ successfully established this as a fallacy by testing 180 children in the St. Louis Children's Hospital with intradermic tuberculin and diphtheria toxin, and by finding similar reactions in only 34 cases.

Influence of Pregnancy on the Reaction.

Report on a series of 50 maternity cases. With the exception of three or four all the tests were made during the first week of the puerperium, the babies' ages varying from two to eight days.

Mother and baby negative	...	...	...	45
Mother and baby positive	...	...	...	1
Mother negative, baby positive	...	...	...	1*
Mother positive, baby negative	...	...	...	3

* Reaction doubtful (baby 4 months).

That is, 90 per cent. of the mothers, and 95 per cent. of the babies, gave a negative reaction. Controls were done at the same time with toxin which had been heated to 75° C. for ten minutes. We found that no less than 30 (that is, 60 per cent.) of the mothers gave pseudo-reactions, 27 of them occurring in the immune mothers and 3 in those who gave positive Schick reactions. Three of the 27 who showed a pseudo-reaction had had diphtheria in infancy.

The actual technique in newly-born infants presented some difficulty, but only those results have been used in which a quite satisfactory injection (showing the well marked white wheal, etc.) was made. The natural

erythema of a young infant's arm rendered one or two readings doubtful at first, but complete absence of pigmentation or scaling at the end of a week led one to the diagnosis of a negative reaction.

Finding 90 per cent. of negative reactions in puerperal women as compared with the 75 per cent. quoted by Schick in the records of the Willard Park Hospital, and the 67 per cent. found by myself in scarlet fever patients, raises once more the long-vexed question of the possibility of pregnancy conferring temporary immunity to disease. It is, however, quite impossible, in a short paper such as this, to enter into the controversial literature on that subject.

The large number of pseudo-reactions (90 per cent.) found among pregnant women, I think, endorses the view that the pseudo-reaction is of the nature of a local anaphylaxis, the woman in this instance being sensitized by the protein absorbed through the placenta.

Immunity in the New-born.

In the 50 odd cases tested only one baby gave a definitely positive reaction, and one in a 4 months baby was doubtful. Schick, however, found 7 per cent. of positive reactions in a series of nearly 300 tests made on new-born infants. According to Zingher,⁶ the antitoxin of the infant obtained from the immune mother lasts for about six to nine months after birth. Kazzowitz and Groer⁶ found that 84 per cent. of mothers and their new-born infants contain a body which has the property of neutralizing diphtheria toxin, and this they identified with diphtheria antitoxin. This is present in mothers and infants, and, presumably, is transmitted through the placenta to the foetus, and because of its frequency is regarded as a physiological phenomenon. The fact that children of the same family give the same reaction also suggests an hereditary factor, which in the absence of infections by the Klebs-Loeffler bacillus gives rise to the presence of the so-called natural antitoxin. That nearly all infants are born with a sufficiency of antitoxin to render them immune to diphtheria is an established fact; why it should persist in some children and disappear in others is still unexplained. Zingher tells us that only a few infants retain their maternal immunity after the twelfth month, and probably all lose it before the eighteenth month of life.

Our next consideration is that of the establishment of an artificial immunity, which will replace or supplement the natural, and carry the child safely through those years when he is most susceptible to the disease.

Active Immunization of Infants.

As the immunity conferred by the mother varies in the length of time it persists—disappearing in most cases at the end of six months, yet persisting in some children till the end of the second year of life—it is obvious that a negative Schick reaction is not reliable until after the second year. Park and Zingher⁷ adopted the following procedure in institutions:

Infants six months or more in age were Schick-tested. If positive they were immunized by injecting subcutaneously three doses of toxin-antitoxin mixture. Those giving a negative Schick reaction were retested every three months up to the third year because of the gradual loss of passive immunity in many. Those giving a positive test at any time were immunized. After the administration of the immunizing doses (work done by Dr. Blum) immunity developed in from three weeks to three months, and lasted more than two and a half years.

Speaking at the New York Academy of Medicine in 1918 Zingher said: "In children over 2 years of age a negative Schick test indicates a permanent immunity to diphtheria. Fully 99 per cent. of the children over 2 years of age who give a negative Schick reaction continue, when retested at a later period, to give a negative reaction."

He finds that those who gave a positive Schick reaction and were injected with toxin-antitoxin were slow in producing antitoxin. Only 30 per cent. were found to be immune at the end of three weeks, but the Schick test in the other children became fainter and fainter and eventually became negative in most instances.

Later Schick tests showed that 95 per cent. of these children had become immune. He has also immunized children by three doses of toxin-antitoxin and found that they gave negative Schick reactions when retested two and a half to three years later. He recommends that all positive reactors under 18 months be given three doses of toxin-antitoxin, each of 0.5 c.cm., one week apart; and that of the children over 18 months of age, and of adults, only those who give a positive reaction

should be immunized with toxin-antitoxin. They should have three doses of 1 c.cm. one week apart. Young children show no reaction.

In 1916 Park and Zingher⁸ presented a paper based on a series of over 1,000 cases that had been actively immunized with diphtheria toxin-antitoxin. These susceptible individuals were selected by means of the Schick test out of a total of about 10,000 children and adults in ten different institutions. The mixtures of toxin-antitoxin that were used for immunization were either neutral (66 to 70 per cent. L. + to each unit of antitoxin), or slightly toxic (80 to 90 per cent. L. + to each dose of antitoxin) to the guinea-pig. The dose was varied from 0.5 c.cm. to 1 c.cm. and the number of injections from one to three. The injections were made subcutaneously at intervals of seven days.

The retests with the Schick reaction showed that only 30 to 40 per cent. became immune three weeks after the first injection, about 50 per cent. at the end of four weeks, 70 to 80 per cent. at the end of six weeks, and 90 to 95 per cent. at the end of eight to twelve weeks.

The best results were obtained with the full immunization consisting of three injections of 1 c.cm. each, given at weekly intervals. The duration of the active immunity was studied in a group of children that was followed up for over one and a half years; these cases showed that the active immunity persisted for at least that length of time. It is possible that the immunity induced by the injections of toxin-antitoxin started a combined cellular production of antitoxin, which would have otherwise appeared much later in life. The L. + dose of toxin is the amount which, when mixed with 1 unit of antitoxin and injected into a 250-gram guinea-pig, will cause its death at the end of four days.

Conclusions.

1. The Schick test has given us very definite data as to which years are the most dangerous with regard to diphtheria infection in a child's life. These are between 6 months and 6 years, while the periods of lowest susceptibility appear to be under 6 months and over 15 years. These results are endorsed by clinical experience.

2. It is of great value in deciding the difficult question of whether a patient is a carrier or is really suffering from diphtheria. For example, a case of streptococcal tonsillitis in a diphtheria carrier would by culture alone be thought to be one of diphtheria. If a Schick test were done on such a case no doubt would be left—in the case of the test being negative it would be treated as a carrier, and if the reaction were positive, as a case of diphtheria. Similarly in a case with a nasal purulent or sanious discharge the same difficulty would arise and a Schick reaction here too would indicate the line of treatment to be followed.

3. It has, perhaps, its greatest value in showing us to whom, among persons exposed to infection (for example, contacts, doctors and nurses), we may safely omit to give antitoxin—thus greatly minimizing the risk of anaphylaxis and also saving pain and expense. When possible, only those nurses who give a negative Schick reaction should be employed in diphtheria wards.

4. We are able by means of the Schick test to ascertain, in cases which have previously had the disease or have had antitoxin, to what extent their immunity persists, and whether they have sufficient antibodies to overcome a fresh infection.

5. Lastly, it has supplied us with a basis on which to build new immunizing methods, which have given such encouraging results in America that we feel justified in looking forward with confidence to the day when diphtheria will be a disease well under our control, and the infant and child life of this country robbed of one of its chief horrors.

I wish to express my thanks to Dr. Claude B. Ker for his guidance in doing this work, and for permission to publish the results. I also wish to thank Dr. Stewart Fowler, Dr. Lamond Lackie, and Dr. H. Gibson for giving me opportunities of carrying out the tests in their respective wards.

REFERENCES.

- ¹ Schick, B., *Muench. med. Woch.*, 1913, ix, 2608. ² Leete, H. M., The Schick Reaction, *Lancet*, January 24th, 1920. ³ Zingher, *Amer. Journ. Dis. Children*, 1917. ⁴ Moody, Ellsworth, *Journ. Amer. Med. Assoc.*, 1915, lxiv, 15. ⁵ Zingher, *Amer. Journ. Dis. Children*, 1918, xvi, 19. ⁶ Kazzowitz and Groer, *Jahrbuch für Kinderheilkunde*, 1913. ⁷ Park and Zingher, *New York Med. Record*, 1918, xciv. ⁸ Park and Zingher, *New York Med. Record*, 1916, ix. ⁹ Park and Zingher, *Archives of Pediatrics*, xxi, 481.

A MONUMENT was recently erected in one of the public parks of Madrid to Dr. C. M. Cortezo, the Spanish physician and politician, who is editor of the *Siglo Médico*, in recognition of his long philanthropic and public activities. At the inauguration ceremonies, in response to many speeches, Dr. Cortezo said that he accepted the tribute only as homage to the medical profession.

THE TREATMENT OF SYPHILIS IN MACEDONIA ON ACTIVE SERVICE.

BY

TREVOR HAYMAN FOWLER, M.R.C.S., L.R.C.P. LOND.,

CAPTAIN (LATE R.A.M.C.),

LATE SPECIALIST IN VENEREAL DISEASE, BRITISH SALONICA FORCE.

THE experience of four and a half years in the army, the greater part of which time was spent in the diagnosis and treatment of venereal diseases, may justify a few remarks upon the methods employed in dealing with syphilis in Macedonia during the late war. I soon became impressed, first, with the importance of making a definite diagnosis as early as possible, and secondly, with the danger of the policy of applying local treatment to a venereal sore and awaiting results.

The hospital for venereal diseases contained some 300 beds, of which roughly a third were set apart for patients suffering from syphilis. Cases admitted to hospital with no other signs beyond a venereal sore were treated as follows: The sore was scraped and the exudate transferred to a microscope slide, a film made, stained by the Giemsa method, no other being at our disposal, and examined. If deemed advisable, the blood serum was tested by the Wassermann reaction, which was regarded as a help to diagnosis, but not relied upon alone, nor was it allowed to outweigh clinical evidence. Cases which left no room for doubt clinically were not necessarily subjected to the microscopic search for the *Spirochaeta pallida*, or to the Wassermann test. It is well perhaps to mention this fact, because in an article which appeared in the *Practitioner* for December, 1920, upon the Wassermann reaction, by Dr. C. Lundie, it was stated that in the army "a diagnosis of syphilis is not allowed, except when the *Spirochaeta pallida* is found or the Wassermann reaction is positive, and *per contra*, a cure is not admitted until both have become negative, a result in the case of the Wassermann sometimes impossible to attain."

The diagnosis having been made the patient was at once put under treatment, the usual course consisting of:

- (1) A weekly injection (intramuscular) of mercury.
- (2) Daily mercurial inunctions.
- (3) A weekly injection (intravenous) of "606" (salvarsan, kharsivan, diarsenol, galy), 0.3 gram, or a fortnightly injection 0.6 gram.
- (4) The urine was tested weekly, and treatment regulated thereby.
- (5) The patient was weighed at the commencement of treatment and at stated intervals throughout the course.

A rigid régime was insisted upon before and after the "606" injections; the reaction was usually slight, sometimes there was none. No cases of arsenical dermatitis occurred, and no suppurations ever followed the mercurial injections. Iodides were frequently given, but they did not form a part of the routine treatment. They were never used except in conjunction with mercury, not being regarded in themselves as a cure for syphilis.

Patients who had had repeated attacks of malaria, or who had suffered from dysentery or severe diarrhoea, and who had become debilitated thereby, did not make good subjects for this intensive treatment. As a rule mercury was withheld in these cases, at first altogether, and "606" administered in doses of 0.3 gram. If, as was usual, improvement took place, mercury was injected cautiously, a careful watch being kept for albuminuria or diarrhoea. A great many cases showed a mixed infection, due either to superimposed sepsis, or to the original sore containing pyogenic organisms. Suppurating inguinal glands were treated by simple surgical methods and were incised when "ripe"; at one time the plan of excising the glands before the skin had become involved was adopted; we found it tedious and without any appreciable advantages. The average stay of a patient in hospital was five to six weeks.

Each patient on leaving hospital was given a slip of paper which he was told to hand to his medical officer; whether this was always done is open to doubt. The advice given was to take one pill of hyd. c. cret. gr. ij each night for three months, to leave off for one month, and at the end of that month to have the blood tested by the