

THE SCHICK REACTION, WITH RECORDS OF 400 TESTS.

Thesis for the Degree of M.D.

by

GLADYS WARD, M.B., Ch.B., D.P.H.

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My grateful thanks are due to Dr Claude Ker, City Fever Hospital, Edinburgh, for his guidance in the technique and reading of the reaction, and also for his permission to perform tests in two of his Scarlet Fever Wards and to reproduce the results. He has also supplied me with the toxin throughout.

Also I wish to express my thanks to Dr Stewart Fowler for his permission to use the cases in the Dundas Ward of the Sick Children's Hospital, to Dr Lamond Lackie, for allowing me to do Schick's tests on such patients in the Maternity Hospital, as were willing to have it done, to Dr Ballantyne and Mr Graham for giving me facilities to study in the Royal College of Physicians Library, and to Dr Gibson for permission to do a certain amount of work in Craiglockhart Poorhouse Hospital.

This Thesis may be conveniently subdivided under these headings.-

- (1) Preparation of the Toxin and technique of the Injection.
 - (2) Reading and Interpretation of Results.
 - (3) Influence of Age on the Schick Reaction.
 - (4) Influence of Concurrent disease.
 - (5) Influence of Antitoxin injections and of previous attacks of Diphtheria.
 - (6) Influence of Pregnancy on the Schick Reaction with references to immunity during Pregnancy.
 - (7) Relation between pseudo-reactions and pregnancy.
 - (8) Immunity in the New Born.
 - (9) Active Immunization.
 - (10) Practical Applications of the test.
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(1) PREPARATION OF THE TOXIN AND TECHNIQUE
OF THE INJECTION.

The Diphtheria toxin, for use in the Schick Test, consists of a broth culture of the Diphtheria Bacillus, which has been grown in the thermostat at 37° C. for six days. To kill the living organisms 10 parts of a 5% solution of phenol are then added, and the bacteria allowed to sediment by keeping the broth culture in the ice box during the following two to three days. The supernatant culture fluid is now passed through a Berkefeld Filter and the clear filtrate of toxin standardized. This is only a preliminary standardization. Since a considerable part of the toxin is converted into toxoids during the succeeding 12 - 18 months we have to use, for purposes of the Schick test, a toxin that has been ripened for at least a year, and then carefully standardized by determining the minimal lethal dose of the toxin for a 250 gramme guinea-pig. The bulk toxin will keep its strength very well if a ripened toxin is used. A primary dilution of the toxin is made until we have a diluted toxin containing one-tenth of a minimal lethal dose in 1 ccm.

The/

The amount actually injected in the test is 0.2 ccm. of this dilution, i.e. one-fiftieth of a minimal lethal dose.

To make the injection it is essential to have a short, sharp, short-bevelled needle, which fits accurately on the syringe. A 1 cc. Record Syringe was 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 just cleaned with a little ether or spirit, the skin is made taut with the forefinger and thumb of the left hand, and one-fifth of a ccm. of the diluted toxin is injected intracutaneously. The result is absolutely useless if the injection be made subcutaneous. 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.

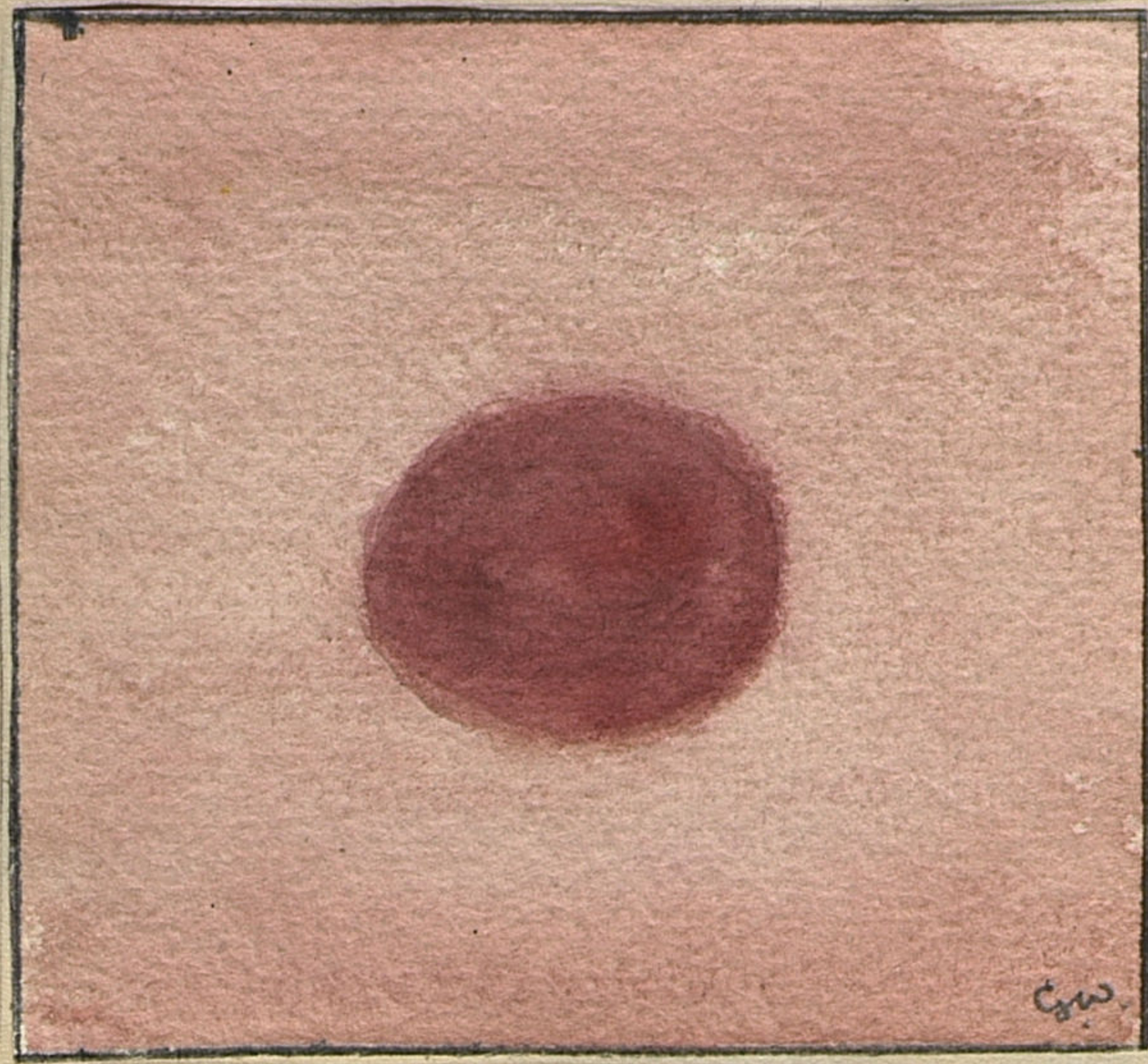
The majority of the readings referred to in this paper were made at 24 hour, 76 hour and 7 day intervals. The reasons for these intervals are as follows.-

(a) At the end of 24 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 48 hours, and by the time 76 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 former is quite reliable and it is certainly more convenient when dealing with patients in a general hospital.

"Control" tests were made on the left arm at a corresponding point to the site chosen on the right arm.



A true positive Reaction.



A Pseudo Reaction.

(2) READING AND INTERPRETATION OF RESULTS.

A true positive reaction is clearly visible at the end of 24 hours, as a clearly circumscribed red area, generally about $\frac{1}{2}$ " 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 entirely. 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 24 - 36 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 36 hours and has generally quite disappeared at the end of 76 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/

Combined Positive and Pseudo Reaction.



general reaction has been noted (headache, vomiting etc.). These cases, however, are the exception.

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 reading of the different reactions, after a short apprenticeship, presents little difficulty except in cases complicated by a pseudo-element. Should the clinical differences be insufficiently marked to enable us to decide between a "positive", a "pseudo", and a combined "pseudo" and "positive", a "control" should be done on the other arm. 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. By this means we are able to compare the reactions in the two arms and should have no difficulty in drawing our conclusions.

It has been found convenient to use the following signs.-

Should a case when first seen show a faint reaction which is difficult to interpret it is entered as + or † according to whether it has the appearance of becoming a — or a + later.

At/

At the second reading it is usually possible to record a — or + definitely. At the third and final entry all three readings are considered. The degree of reaction may be expressed by + , ++ , or +++ .

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

It is of course essential that the toxin be reliable. Over 50 results of tests made at the City Fever Hospital and elsewhere had to be rejected as it was found that the percentage of negative reactions was unduly high, and the toxin when subsequently tested by Dr Ker was found to be weak and therefore entirely unreliable.

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 neutralise the toxin, and is therefore immune to the disease at the time when the test is made.

According to Schick² himself, a negative reaction indicates at least $\frac{1}{30}$ of a unit of antitoxin per cc.

of/

of blood, i.e. sufficient to protect against Diphtheria. Von Behring maintains that $\frac{1}{100}$ unit is sufficient. A Positive Schick indicates that the individual tested does not contain sufficient Antitoxin in his blood to render him immune to the disease. A Pseudo reaction is probably a local sensitization phenomenon of a protein character, since a similar reaction can be produced with toxin heated to 75° C. for five minutes, or with dilutions of the autolysed substance of the Diphtheria Bacillus in which no toxin is present.

Zingher, writing in 1917 in the Archives of International Medicine, says:-

"The pseudo reaction depends on a hypersusceptibility of the individual's tissue cells to the autolysed protein of the Diphtheria Bacillus, which is present in the toxin broth used for the test. The reaction is therefore of the nature of a local anaphylaxis."

Kolmer and Moshage⁴ in the Journal of the American Medical Association write as follows:-

"We would ascribe pseudo reactions to the following:- To local anaphylactic reactions of a general protein character, as described by Park. We subscribe to this view, principally because of certain experimental data at hand indicating that general proteolysins are present in the body fluids which/

which may digest such general protein substances as are contained in broth, or the protein substances may serve to saturate the unsaturated fatty acids (antitrypsin) of the blood serum followed by a release of tryptic activity and digestion of the patients own serum protein (Jobling, Petersen and Bronfeu-:brauner) with the formation of proteo-toxins capable of producing local reactions of redness and oedema. The majority of the Schick tests with controls were conducted with persons in the Measles, Scarlet Fever and Diphtheria wards of the Philadelphia Hospital for Contagious Diseases; a number were among patients in the isolation and children's wards of the Philadelphia General Hospital. Scarlet Fever and Diphtheria patients had received antitoxin prior to the tests, while of the patients ill of Measles, only those giving true reactions were immunized with antitoxin.

The great majority of Pseudo reactions appear to be due not so much to the injury of the Epidermis by the needle and the fluid injected, as to a peculiar hypersensitiveness of the skin in certain individuals.

This hypersensitiveness was found most evident among persons in the various stages of Scarlet Fever. It was also more apparent among children who had Measles/

Measles than among normal children. Of 103 persons in the Scarlet Fever wards receiving an intradermic injection of the same amount of bouillon (.0002 cc.) as contained in the toxin, about 60% showed a false reaction at the end of 18 hours, while at the end of 48 the reaction persisted in but 7%, and in 72 hours in but 2%, the latter showing a pseudo reaction corresponding to the description given by Park and his associates.

A number of Scarlet Fever patients had received 2,500 units of antitoxin within 10 days prior to the time these tests were made, and it was particularly apparent that some persons showed no reaction at all with either toxin or control fluid, while of those showing a reaction the size, general appearance and duration of each reaction were almost identical with the toxin and bouillon control injections.

This peculiar skin hypersensitiveness among persons who have Scarlet Fever or who had just recovered from infection is shown by the large percentage (46%) of similar reactions following the intradermic injection of .05 cc. of sterile normal salt solution containing .25% tricresol. After 24 hours these reactions rapidly and entirely disappeared. Among normal persons this injection was practically always/

always without effect."

In the 150 cases tested in the Scarlet Fever wards of the Edinburgh City Fever Hospital, 14 showed pseudo reactions (9.4%) and of these only one had previously had antitoxin.

(3) INFLUENCE OF AGE ON THE SCHICK REACTION.

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

Age.	Number.	Neg.	Pos.	%†
.0 - $\frac{6}{12}$	25	23	2	8
$\frac{6}{12}$ - 2	41	21	20	50
2 - 5	20	10	16	61
5 - 10	44	30	14	34
10 - 15	14	10	4	28
Total	150	94	56	37

From this we see that the greatest number of † Schicks occurred in children between the ages of $\frac{6}{12}$ and 5. This we know to correspond to the age incidence of Diphtheria. Zingher obtained from 32 to 17 per cent of positive reactions in children varying from two to sixteen years.

The following is 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% of the total number of deaths occurred between the ages of one and five years.

(4) INFLUENCE OF CONCURRENT DISEASE ON THE REACTION.

Table of results in the Scarlet Fever Wards.

Age.	Number	Neg.	Pos.	% + .
0 - 1	0	0	0	0
1 - 2	2	0	2	100
2 - 5	17	0	17	100
5 - 10	47	21	26	55.3
10 - 15	30	11	19	63
15 & 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 accurately with those done in the City Fever Hospital last year and published by Dr Leete⁵ in the Lancet, Jan. 24, 1920.

I have here reproduced his table.

Age.	Number	Neg.	Pos.	% + .
1 - 2	8	0	8	100
2 - 4	41	9	32	78
4 - 6	90	27	53	59
6 - 8	93	39	54	58
8 - 15	190	84	106	56
15 & over	88	55	33	37.5
Total	500	214	286	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% between the ages of $\frac{6}{12}$ and 15 years were positive; in the latter 37%.

For a long time, moreover, it has been a recognised fact that, in spite of all precautions, cases of Diphtheria occur in the Scarlet Fever Wards more readily than in other wards. Zingher⁶ suggests that "there may be a destruction of the natural Diphtheria antitoxin during an attack of Scarlet Fever. Von Behring has suggested that there is a temporary loss of the natural immunity to Diphtheria during the acute febrile stage of the disease. This loss is caused, according to Von Behring, by a destruction of the small amount of natural antibodies, present in some individuals, which is just sufficient to give a negative Schick. This does not appear to occur during an attack of Measles, but has been recorded as occurring during Poliomyelitis. From these facts we may gather that a child who is susceptible to the more rare disease of poliomyelitis would be more likely to give a + Schick.

Similarly in Scarlet Fever, since Scarlet is only about one-fourth as contagious as Measles we would/

would expect to find a higher percentage of positive Schicks among Scarlet than among Measles patients."

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 Schicks is given under the following headings. Those cases, only, were chosen which, quite definitely, were able to be classified. The percentage refers to the total number tested.

1. Respiratory Diseases (not T.B.)	56.25%	gave	+	Schicks.
2. Alimentary Diseases (not T.B.)	50%	"	"	"
3. Tuberculosis	45.5%	"	"	"
4. Nervous Diseases	33 $\frac{1}{2}$ %	"	"	"
5. Rheumatism (including Chorea)	27%	"	"	"
6. Rickets	16.6%	"	"	"
7. Kidney and Bladder	16.6%	"	"	"
8. Congenital Syphilis	14%	"	"	"

Another series of cases was then taken and divided/

divided into two groups - acute and chronic; care again being taken to exclude entirely all such cases as could not be definitely classified.

The "chronic" cases included:-

Chronic tuberculous infection of Abdomen.

" " " " Lung

" " " " Kidney

Long standing Empyemas.

Congenital Syphilis, etc.

while the "acute" were made up chiefly of:-

Pneumonia

Acute Bronchitis

Acute Gastro Enteritis

Acute Nephritis, etc.

The results were as follows:-

Of 'Chronic' cases 28% were positive

72% " negative

Of 'Acute' cases 60% " positive

40% " negative

We see, therefore, that the number of positive Schicks found in the 'acute' cases was as high as those found among Scarlet Fever patients. The figure given by Dr Leete, in the 500 cases quoted by him in the City Fever Hospital, shows that between the ages of 1 and fifteen, 60% were positive. My own figure is/

is somewhat higher, viz. 67%. 'Acute general' cases of the same ages also gave 60% positive Schicks.

It would seem from this that any extra, sudden strain thrown upon the child's symptom produces a lowering of resistance to other diseases because all its reserve of strength becomes absorbed in manufacturing the specific antibodies required at the moment. This is in accordance with the well known fact that a child already suffering from one acute disease, if attacked by another, is more likely to succumb than is a healthy child attacked by the same disease. On the other hand it would appear that a child suffering from a slowly developing disease has more time to arm for the fray; and, at any rate, at a certain stage of the infection, has probably a higher resistance to all disease than has the normal child! It was interesting to note 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 affected and left hospital "improved" gave a negative reaction.

Another interesting point, which has its bearing on the above question, was supplied by two sisters who were in the ward at the same time suffering from Dysentery. One was aged 7, and the other 8, and neither/

neither of them had had Diphtheria. The infection in both cases was by a Shiga Bacillus.

The younger, who was the more severely ill on admission and subsequently died, gave a strongly positive Schick, whilst the elder, who was only mildly infected and made a good recovery, gave a negative. It has been noted by various observers that immunity or non-immunity to Diphtheria runs in families. Bundesen remarks.- "We found that children of the same family invariably gave a similar reaction. They were all negative or all positive." Such also has been my own experience. Is not this very suggestive then of the fact that any acute infection may cause a temporary loss of natural immunity? This is also in keeping with Von Behring's hypothesis (already quoted) with regard to Scarlet Fever.

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 Moody², I think, 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 thirty-four cases.

(5) INFLUENCE OF ANTITOXIN ON THE REACTION.

Under the heading "Abolition of the Reaction by Antitoxin, Dr Leete⁵, in the same article as has been referred to before, writes: "One hundred and ten cases, all of whom had previously received therapeutic doses of antitoxin at periods varying from 1 to 70 days before the performance of the test, were tested, and all except one gave a negative result. The exception was a rather doubtful positive showing redness at 48 hours and faint pigmentation at 10 days. It occurred in a child of six years who had received 8000 units of antitoxin 26 days previous to the test. A remarkable feature was the large number of pseudo-reactions which appeared in these passively immunised patients. Sixty-one in this series were controlled with heated toxin and of these 44 (72 per cent) gave a definite pseudo reaction. In a series of 104 controlled cases on the Scarlet Fever side only four showed pseudo-reactions. It would appear that the serum had sensitized the individuals and rendered them hypersensitive to the proteins of the toxin. A few cases among the Scarlet Fever patients which gave good positive results received 500 units of antitoxin and were re-tested next day. Of 15 cases so treated all/

all gave negative results, though three showed pseudo-reactions". Zingher^s found that the period of immunity induced by 1,000 units of antitoxin varied from 21 to 25 days, though he occasionally obtained a positive reaction at the end of 15 to 18 days. "The effect", he writes further, "of a previous injection of antitoxin upon the duration of passive immunity, as given by a second dose of antitoxin, can be studied in a very interesting way by using the Schick reaction." According to von Behring, a primary injection of 1,000 units of antitoxin will protect for three weeks, whereas a secondary injection of a similar amount, given at a time when the body is still sensitized by the first injection, will protect for only 5 to 8 days. This increased destruction of antitoxin is attributed by von Behring to the production in the body, as a result of the first injection of the antitoxic horse-serum, of a proteolytic ferment, which causes a more rapid breaking down of the second dose of antitoxin. Römer and Viereck have shown the same increased destruction of antitoxin in sensitized animals. "About 150 children who gave positive Schick reactions were immunized with 1,000 units of antitoxin. At the end of 30 days they were retested and a positive reaction again obtained. These children were then reinjected with a second dose of/
of/

of 1000 units of antitoxin, and we now found that fully 60 per cent had destroyed the second dose in 7 days, and another 10% in 10 days. The fact that repetitions of the immunizing dose give, in a majority of cases, much shorter periods of protection than the first injection, makes it difficult to prolong the period of passive immunity."

On this evidence we may conclude that therapeutic doses of antitoxin may confer a passive immunity which occurs well within the first 24 hours of the first injection and persists probably as long as 70 days, certainly as long as 30. I say probably as long as 70 days, not knowing whether the case quoted by Dr Leete as having had antitoxin 70 days previous to giving a negative Schick, had originally given a positive Schick or not. I have had no personal experience in this matter further than by observing the way in which the Schick reaction was influenced by antitoxin given either immediately before, or during the time of reading the test.

Case I. W. W. S.

Test made	12. 1. 20.
1st Reading	13. 1. 20. —
2nd "	14. 1. 20 —
Antitoxin 5000 units given	16. 1. 20.
Final.	21. 1. 20. —

Case 2. H. H. 17.

Test made	12. 1. 20.	
1st Reading	13. 1. 20	<u>+</u>
2nd "	14. 1. 20	+
19.1.20	Positive throat. No clinical symptoms.	
	500 units antitoxin given.	
Final	21. 1. 20	+

This does not correspond with Dr Leete's experience that giving 500 units produced a negative Schick within 24 hours. It was among one of the first cases done by me, and I might have been led to think the error lay either in my technique or my judgment, had not both the injection and the readings been made under the supervision of Dr Leete himself. The only possibility that suggests itself is, that had a Schick test been done the day after the antitoxin was given it might have been negative, and the immunity may have passed off in the ensuing three days. This, however, is difficult to imagine in view of the fact that the patient showed no clinical symptoms.

Case 3. Nurse R.

3000 units Antitoxin	given	21.12.19.
Test made		13. 1.20.
1st Reading		14. 1.20 + Pseudo?
2nd "		15. 1.20 Pseudo.
Final		22. 1.20 Negative.

Case 4. N. J.

Test made 28. 1. 20.

6000 units Antitoxin given the same day.

1st Reading $\frac{+}{-}$

2nd Reading $\frac{+}{-}$

Final —

Case 5. B. M. 9.

3000 units Antitoxin 1.2.20.

Test made 3.2.20

1st Reading 4.2.20 —

2nd " 5.2.20 —

Final 12.2.20 —

Case 6. E. F. 6.

3000 units Antitoxin 2.2.20.

Test made 3.2.20

1st Reading $\frac{+}{-}$

2nd " $\frac{+}{-}$

Final —

In every case, except No.2, the final reading was negative.

An attack of Diphtheria does not confer a lasting immunity.

Park and Zingher⁸ attempted to trace a number of the patients who had had definite tonsillar exudates with positive cultures. Thirty-two such patients, who had been treated at the Willard Parker Hospital 3 - 4 months before, were tested by Dr Rosenberg during an investigation of discharged contagious disease cases. Nineteen of the 32 gave positive Schick reactions while 13 were negative. Fifteen children were also tested. Seven of the 15 had had diphtheria about one year before; of these 5 gave positive and 2 negative reactions; eight cases had had the disease about 4 months previously, and, of these, 7 gave positive and one a negative reaction.

At the Willard Parker Hospital 4 patients were tested who were suffering from a rather mild type of diphtheria; three tonsillar and one nasal. The Schick reactions were strongly positive on admission - no antitoxin was given, and the exudates cleared up at the end of 4 - 5 days. Tested with the Schick reaction two days after the disappearance of the exudate, it was again found strongly positive in every case. A similar strong reaction was obtained two/

two or three weeks after the disease. These children had evidently developed little or no antitoxic immunity, and yet they made an uneventful recovery.

Chronic tube cases, on the other hand, who had been in hospital for more than a year generally showed a negative reaction. Patients who had had Diphtheria recently (2 - 3 months) frequently gave a positive reaction which became negative if they remained in hospital for another 5 - 6 months. Three children who had had diphtheria in March 1914 were tested about the middle of August 1914. One gave a negative, one a moderately positive, and one a strongly positive reaction. They were retested $2\frac{1}{2}$ months later, and the following results were noted: The negative case remained negative; the moderately positive reaction showed a very faint reaction; while the strongly positive case gave a much weaker reaction at this time. When they were tested again two months later, i.e. eight months after the illness, they all gave a negative reaction, and blood examinations showed the presence of antitoxin."

They conclude that Diphtheria patients develop as a rule an anti-bacterial immunity, which is associated in only about one-third of the cases with an antitoxic immunity; and, further, they conclude that/

that chronic reinfections with the Klebs-Loeffler bacillus, as seen in children who remain a long time in the diphtheria wards, appear to finally lead in a majority of cases to the production of an antitoxic immunity.

Ten cases of people who had had Diphtheria cropped up in my series of cases. The reactions were as follows:-

- | | | | | | |
|-----|--------|-----------|---------|------|----------------|
| (1) | Mrs A. | Had Diph. | 18 yrs. | ago. | Neg. & Pseudo. |
| (2) | M. D. | " | " | " | Negative. |
| (3) | Mrs G. | " | 10 yrs. | " | Neg. & Pseudo. |

(These three were done during puerperium.)

- | | | | | | | | | |
|------|-----------|----------------|---|---|----------------|---|---|----------------|
| (4) | M. T. | 6. | " | " | $\frac{5}{12}$ | " | " | Strong + |
| (5) | C. P. | 18 | " | " | 8 | " | " | Neg. & Pseudo. |
| (6) | K. J. | 19 | " | " | 10 | " | " | Neg. & Pseudo. |
| (7) | H. M. | $2\frac{1}{2}$ | " | " | $\frac{6}{52}$ | " | " | Positive. |
| (8) | A. D. | 4 | " | " | $\frac{6}{52}$ | " | " | Negative. |
| (9) | B. B. | 9 | " | " | 2 | " | " | Neg. & Pseudo. |
| (10) | Sister L. | | " | " | $\frac{6}{12}$ | " | " | Neg. & Pseudo. |

We see from this that of the three children who were in the most susceptible age period, viz., M.T., H.M., and A.D. (all of whom had had the disease recently), two gave well marked positive reactions and one gave a negative. All the remaining seven showed complete immunity.

(6) INFLUENCE OF PREGNANCY ON THE SCHICK TEST.

Report on a series of 50 Maternity cases, chiefly drawn from the Simpson Memorial Hospital.

With the exception of three or four, all the tests were made on women during the first week of the puerperium, the babies ages varying from two to eight days.

The results were as follows:-

Mother Neg. Baby Neg.	Mother Pos. Baby Pos.	Mother Neg. Baby Pos.	Mother Pos. Baby Neg.
45	1	1 doubtful (Baby $\frac{4}{12}$)	3.

i.e. 90% of the Mothers gave Negative reactions.
96% " " Infants " " "

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 (i.e. 60%) 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 toxin which was being used in these tests was also/

also being used elsewhere in testing patients in a general hospital, and in these cases there was no increase in the percentage of pseudo reactions, and that of the negative reactions was normal.

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.

To recapitulate, we found 90% of Negative and no less than 60% of pseudo reactions among puerperal women, and 96% of negative and no pseudo reactions among newly born infants.

To deal first with the point - the large number of negative results in puerperal women.-

Finding 90% of negative reactions in puerperal women as compared with the 75% quoted by Schick in the records of the Willard Park Hospital, and the 67% found by myself in Scarlet Fever patients, raises once more the long vexed question of the possibility of pregnancy conferring immunity to disease. Though it/

it is not possible to go fully into all the controversial literature on this subject now, there are one or two articles to which I should like to refer.

Amand Routh¹⁰, in an article entitled "The Influence of Pregnancy on the prognosis and treatment of coexisting acute and chronic disease", considers this matter fully under the headings of various diseases.

Under "Enteric Fever" we find.-

"Rokitansky believed that pregnancy gave a sort of immunity from Typhoid, and although Jenner and Murchison disagreed with this view, it seems probable that a pregnant woman is less liable to be infected, at all events in the late months, for the great majority of cases of typhoid in pregnancy occur in the first half of gestation. Typhoid during the latter months is probably more serious than in the earlier months.

Under "Influenza".-

There seems to be reason to believe that pregnant women are somewhat immune from influenza, for such a complication is rarely seen, and lying-in hospitals in England have almost always escaped the disease even when influenza has been raging all round". It would be interesting to know whether the late epidemic/

epidemic (1918 - 1919) confirmed this view or not.

Under "Scarlatina".-

Scarlatina may, in exceptional cases, complicate pregnancy, and then precipitates labour. In a severe epidemic in Vienna in 1801 all pregnant women miscarried and most of them died. The liability to infection is, however, especially marked shortly before and during the first week after delivery; and at these times the incubation period may be shortened. The mortality of scarlatina in pregnancy is very high, owing chiefly to the great danger of renal complications but during the puerperium scarlatina seems less virulent and "breeds true", pursuing its ordinary course and not producing puerperal septicaemia. A pregnant woman is less susceptible to the infection of scarlatina and, if exposed to infection during pregnancy, some believe that the incubation period may be prolonged to the confinement, but there is no direct evidence to this latter effect. It is a fact, though, that scarlatina during pregnancy is very rare and yet is fairly common during the puerperium. Olshausen was able to collect only seven cases during pregnancy, whilst he collected 140 during the puerperium. Knowing how many cases of puerperal sepsis were diagnosed as Scarlet Fever as recently as/

as twenty years ago (the time of this article), we must regard this more as an interesting instance of the progress of Medical Science, than as a valuable record of facts. We shall later compare this with more modern investigations on the same subject.

Under "Tuberculosis".-

"Pregnant women improve in every way during pregnancy, whilst all organs are, as it were, on the up-grade, but after parturition when degeneration of the hypertrophied organs is in progress, there is usually a very rapid recrudescence of the disease with a hectic temperature."

This also is more of historical than practical interest.

In an article in the B.M.J. 1912, Sir John Byers¹¹ gives weighty evidence that Scarlet Fever during the puerperium is a rarity.

"Personally I believe that scarlatina is rarely met with during the puerperium, because women at that time seem to a large extent to be immune from the disease, either owing to the circumstance that they have had it before, or of the immunity given by age, and that the so-called "puerperal scarlatina" (like most cases of surgical scarlatina) is not really true scarlatina, but rather a form of puerperal infection with a red rash. I have never," he continues, /

continues, "seen in private, or consultation practice, a case in which a woman after childbirth developed Scarlatina, and I have never seen Scarlet in a puerperal woman in the Belfast Maternity Hospital.

Among 16,000 puerperal patients in the Berlin Obstetric Clinique, A. Martin reports that there were three cases of Scarlet.

Dr Gardner Robb gave evidence that in all his fifteen years experience at the Belfast City Fever Hospital and at the Union Fever Hospital, Belfast, he has only seen one case of Scarlatina in a puerperal woman."

Dr Ballantyne, writing along with David Milligan¹² in 1893 commences his article by saying.-

"Scarlatina is an exanthem which is very rarely met with during pregnancy, and some authors have gone so far as to say that the gravid woman is protected from it; but in the case narrated not only did the mother pass through an attack of Scarlet Fever, but the foetus in utero likewise caught the infection."

They record fourteen cases of foetal Scarlatina,- a source of infection was nearly always traced and with the exception of two cases the mothers had not suffered from Scarlet Fever. One case is especially interesting from our point of view as the mother was exposed to contagion two weeks before delivery and did/

did not contract the disease till two weeks after it - the author (Thorburn) says "I can hardly resist the conclusion that the foetus received the poison and suffered its primary effects whilst yet unborn, the mother being then insusceptible, and that she afterwards, owing to the puerperal weakness became susceptible and was infected by her own offspring."

To further quote Dr Ballantyne in an address given to the York Medical Society,-

"Modern science has been investigating the blood reactions of the pregnant condition with much care during these past months, and, whilst it is perfectly true that obstetrics may receive from such researches the gift of a certain blood test for the early detection of gestation, there may also come from them the proof that the carrying of a child in the womb must be classed with the diseases which develop immunity reactions even if it be proved that in some respects pregnancy is an instance of reaction to an antigen, it does not necessarily follow that from all points of view it is to be grouped with diseases."

Further under the heading "Maternal Response in Pregnancy" he continues.-

"It will, however, in all probability be found that upon the blood changes of pregnancy the true theory of/
of/

of the nature of childbearing must rest. By these blood changes I do not mean such simple and obvious alterations as can be seen in increase in white or diminution in red corpuscles, or even in quantitative variations in the iron, albumen or salts of the circulating fluid. I refer rather to the more subtle states which underlie the development of antibodies in response to chorionic or placental antigens, the variations in surface tension as revealed by the Stalognometer, the increased antitryptic power of the serum and the appearance in the blood of ferments or enzymes capable of breaking up placental albumen into peptone and amino-acids. There is no denying the fact that the existence of these reactions on the blood of the pregnant woman, if it can be proved to the satisfaction of the bacteriologist and the clinician, does support the view that gestation has an effect upon the mothers resembling that of an infectious fever and even of malignant disease."

We may therefore, I think, conclude that a pregnant woman may have a higher power of developing antibodies than has the normal individual, and find therefore that our results with the Schick test are not as surprising as would appear at first sight. Whether there is a possibility of using this fact in the treatment of diseases such as Scarlet Fever and/
and/

and Measles, where no organism has yet been isolated, I do not know.

Zingher has had considerable success in the treatment of Scarlet Fever with injections of the blood of convalescent scarlet patients, and it seems to me that the rationale would be the same in the case of the pregnant woman - though her antibodies would not be specialised, her serum might be efficacious where a 'specialised' serum was not obtainable.

(7) RELATION BETWEEN PSEUDO-REACTIONS AND PREGNANCY.

The large number of pseudo reactions found among pregnant women (90%), 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.

In the discussion following Sir John Byers' paper referred to in the last section, Dr Leith Murray of Liverpool, speaking of eclampsia, remarked that very much work had been done in recent years on this aspect (anaphylaxis in pregnancy) of the subject of the immunology of normal pregnancy in general. Mosbacher and several others had produced undoubted evidence that there was homologous sensitization in pregnancy by placental elements. He (the speaker) did not consider that toxic symptoms following were anaphylactic. Cases of phthisis were sensitized to Tuberculin, yet anaphylaxis was not the usual termination.

Dr J.S.C. Douglas (Birmingham) said that the condition of eclampsia may be due to the failure of the pregnant woman to produce antibodies to toxins which are always formed during pregnancy, normal or otherwise, /

otherwise, rather than to the formation of some abnormal toxin. On this supposition the advantage of blood letting in eclampsia may be explained, not so much by the removal of toxins from the blood stream, but by the increased volume of antibodies brought into the circulation by the process: Since it has been shown by von Schroeder that haemorrhage in actively immunised animals was followed by an actual increase in the quantity of antibody present in the circulatory blood.

Presumably the apparent and simple expedient of injecting the serum of a healthy pregnant woman into one suffering from eclampsia has already been attempted, but I have found no literature on the subject. Were it a possible working hypothesis it appears to me that a Schick 'control' test would be of the greatest value in showing which women were likely to afford the most beneficial serum - those containing most antibodies would give a negative reaction. It would be interesting to investigate the reaction in women suffering from eclampsia and the albuminurias of pregnancy.

(8) IMMUNITY IN THE NEW BORN.

In the fifty odd cases tested, only one baby gave a definitely positive reaction, one in a four months baby being doubtfully positive.

Schick, however, found 7% of positive Schicks in a series of nearly 300 tests made on new-born infants. According to Zingher⁹, the antitoxin immunity of the infant obtained from the immune mother lasts for about six to nine months from birth.

The following is his table:-

Age of Infants in months	A. Mother Neg. Infant Neg.	B. Mother Neg. Infant Pos.	C. Mother Pos. Infant Pos.	D. Mother Pos. Infant Neg.
Up to 3	18	1	4	0
3 to 6	19	2	2	0
6 to 9	9	11	1	0
9 to 12	2	10	0	0
12 to 15	4	6	0	0
15 to 24	2	2	0	0
Total	54	32	7	0

Column A shows that thirty-seven out of fifty-four or 68.5 per cent had a negative Schick test during the first six months of life. The negative reaction/

reaction in the nine children between six and nine months of age is probably also due to a continuation of the passive immunity derived from the mother, while in the remaining eight children we may or may not be dealing with such an immunity. Only repeated Schick tests at later intervals could determine this point. The children who were still passively protected would lose their antitoxin in the course of the next few months, and then give a positive reaction; while those whose negative Schick reaction indicated an early developed natural immunity would continue to show a negative reaction.

Column B shows that a large proportion of children belonging to immune mothers have positive Schick tests after the sixth month of life. Twenty-seven out of thirty-two children between 6 and 15 months or 84.3 per cent gave a positive Schick.

Column C shows that in 7 children who gave a positive reaction and whose mothers also gave a positive reaction to the Schick, that if the mother has no immunity none will be present in her infant if it is below 6 months of age.

Column D shows that no case was found in which the mother had a positive and her infant a negative Schick.

Kazzowitz and Groer¹⁴ found that 84 per cent of mothers/

mothers and their new born infants contain a body which has the property of neutralising 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.

Park+Zingher⁸ found that during the systematic testing of groups of children according to families, the children of the same family gave a similar reaction. If variations were found the younger children always gave the positive reactions. If the youngest child had a negative reaction, all the older children were usually negative. On the other hand if the oldest child in the family gave a positive reaction the younger children, with very few exceptions, showed positive reactions.

These striking facts are additional proofs that there are factors, possibly hereditary in character, which, in the absence of infections with the Klebs-Loeffler Bacillus (v. Behring Kleinschmidt), give rise to the presence of the so-called natural antitoxin. The large amount of antitoxin which is present in some of the cases is hard to explain; for example, two young children, $6\frac{1}{2}$ and 3 years of age, who had no history/

history of clinical diphtheria, showed respectively fifteen and nineteen units of natural antitoxin per cc. of serum. The large proportion of older children and adult persons having antitoxin adds to the difficulty of considering the natural antitoxin as usually due to a previous infection with diphtheria bacilli, either as a cause or as a carrier.

That nearly all infants are born with a sufficiency of antitoxin to render them immune to Diphtheria is a well established fact - why it should persist in some children, and disappear within a few months 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.

(9) ACTIVE IMMUNIZATION OF INFANTS.

Having found which infants in a community are susceptible to Diphtheria our next interest is to render them immune.

As the immunity conferred by the mother varies in the length of time it persists - disappearing in most cases at the end of 6 months, yet persisting in some children till the end of the second year of life - it is obvious that a negative Schick is not reliable until after the second year. Park and Zingher¹⁵ have adopted the following procedure in institutions:-

Inmates six months or more in age should be Schick tested. If positive, they should be immunized by injecting subcutaneously three doses of toxin-antitoxin mixture. Those giving a negative Schick 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 $2\frac{1}{2}$ years.

Speaking at The New York Academy of Medicine
in/

in 1918 Zingher said.-

"In children over two years of age a negative Schick test indicates a permanent immunity to diphtheria. Fully 99% of the children over two 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 and were injected with toxin - antitoxin were slow in producing antitoxin. Only 30% 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% of these children had become immune. He has also immunised children by three doses of toxin-antitoxin and found that they gave negative Schicks when retested $2\frac{1}{2}$ to 3 years later. He recommends that all positive reactors under 18 months be given 3 doses of toxin-antitoxin - each of 0.5 cc. 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 1.0 cc. one week apart. Young children show no reaction.

In/

In 1916 Park and Zingher¹⁶ 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 - 70% L+ to each unit of antitoxin), or slightly toxic (80 - 90% L+ to each dose of antitoxin) to the guinea-pig. The dose was varied from 0.5 cc. to 1.0 cc. and the number of injections from one to three. The injections were made subcutaneously at intervals of seven days. The local reactions at the site of injection were generally mild; in the older children and adults the redness and swelling were more marked. General symptoms, like malaise and a temperature of 100° - 102° F. were noted in 10 - 20% of the cases; in a few the temperature reached 104° F. The symptoms lasted 24 - 48 hours and then rapidly subsided. Both local and general symptoms were especially evident in those who showed a susceptibility to the protein by giving a combined pseudo and true Schick reaction. No harmful after effects were noted in several thousand injections.

The/

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

The best results were obtained with the full immunization consisting of three injections of 1 cc. each, given at weekly intervals.

The duration of the active immunity was studied in a group of children that were followed up for over $1\frac{1}{2}$ 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 grm. guinea-pig, will cause its death at the end of 4 days.

For general prophylaxis against diphtheria in schools and communities, excluding immediate contacts, Park and Zingher recommend a mixture of toxin-antitoxin alone (85 - 90% of L+ dose of toxin to each unit of antitoxin) or toxin-antitoxin plus vaccine of/

of killed diphtheria bacilli. The dose is 1 cc. of toxin- antitoxin and 1,000,000,000 bacteria - repeated three times at intervals of 6 to 7 days. They have not yet had sufficient time to judge the value of adding the injections of the bacilli to the toxin-antitoxin.

C O N C L U S I O N S .

The value of the Schick test is now so well established that it seems unnecessary to do more than broadly recapitulate what has already been said.

1. It 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 $\frac{6}{12}$ and 6; while the periods of lowest susceptibility appear to be under $\frac{6}{12}$ and over 15 years. These results are endorsed by our 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. To quote again from Park and Zingher¹⁷.- "With a purulent or sanious nasal discharge it is difficult to decide whether the case is a carrier or a beginning Diphtheria. A negative reaction excludes Diphtheria, while a positive leaves the diagnosis of Diphtheria still a probability. A case of tonsillitis due to streptococcus in a carrier of Diphtheria Bacilli would, by the use of culture alone, be thought to have diphtheria and in danger/

danger of extension of the disease. A negative Schick reaction would indicate the case to be simply a carrier and in no danger from the effects of Diphtheria poison.

3. It has perhaps its greatest value in showing us to whom, among persons exposed to infection (e.g. 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.
4. 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.

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