

THE SCHICK TEST
AND ACTIVE IMMUNIZATION AGAINST DIPHTHERIA
WITH TOXIN-ANTITOXIN MIXTURES

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by

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THE SCHICK TEST

AND ACTIVE IMMUNIZATION AGAINST DIPHTHERIA

WITH TOXIN-ANTITOXIN MIXTURES.

The presence of diphtheria in civilized countries constitutes an important hygienic problem. It shows the need for a practical and efficient active immunization that will protect the child and certain members of our adult population. Such protection should be applied early in life so that an efficient immunity will be produced during that period when the individuals are most susceptible and the disease causes the greatest mortality, that is from one to five years of age.

A few figures showing the number of persons who have suffered from diphtheria in former and recent years in this and other countries will show the need for protecting those who are susceptible to this disease.

TABLE 1.

Number of Cases of Diphtheria notified, 1890-1923, and admissible to the Hospitals of the Metropolitan Asylum's Board, London.

Years	Totals	Yearly Average
1890-9	105,065	10,506
1900-9	86,792	8,679
1910-9	80,929	8,093
1920	Total number	13,797
1921	" "	16,334
1922	" "	15,328
1923	" "	10,374

The actual number of true cases of diphtheria admitted to the fever hospitals of London during 1923 was 7,522, and, out of this number, 5,409 patients were under ten years of age, while more than half of these were under five years of age. The mortality was 6.8 per cent. Dr Foord Caiger⁽¹⁾, commenting on the above figures in the Report, urges that medical practitioners should either administer antitoxin at once or else send the patient to hospital without waiting for the report from the bacteriologist.

In presenting the report of the City Hospital, Edinburgh, for the year 1923, Dr Ker⁽²⁾ notes that 977 patients were admitted to the hospital, and of these 741 were finally diagnosed as true diphtheria.

The percentage mortality of the cases was 8.3 as against 6.6 for the two preceding years. The mortality of the 65 laryngeal cases was 27.6 per cent - a much higher figure than is usual in the hospital. The naso-pharyngeal form of the disease was slightly more fatal, the death rate of 104 cases being 29.8 per cent. Those patients who had the advantage of serum treatment early in the course of their illness had a much higher recovery rate than those who - for various reasons - were unfortunate enough to be treated at a later date. For instance, the percentage mortality of those patients who received antitoxin on the second day was 4.39 as against a percentage mortality of 12.65 of those receiving antitoxin on the fifth day of disease. Dr Ker remarks that while it is satisfactory to note that the case mortality is very different from what it was in the days before antitoxin was used, when it was common for 30 to 40 per cent. of the cases to terminate fatally, it is none the less disappointing to find that the disease is still so serious. Diphtheria is only too often insidious in its onset and the result is that the patient will continue to come into hospital too late to give antitoxin a fair chance, as the figures quoted show. Prevention, Dr Ker remarks, is admittedly better than cure, and he considers it possible that,

in toxin-antitoxin mixtures, we have a reliable means of protecting individuals against diphtheria.

The introduction of the Schick Test has enabled us to distinguish persons susceptible to diphtheria from those who are not, and it is hoped that it may be possible to protect those of tender years who are much more susceptible than those in late adult life.

In the report of the Public Health Department, Edinburgh, 1923, by Dr William Robertson, Medical Officer of Health for the city, it is noted that the number of deaths from diphtheria for the year 1923 was 70, and of these 49, or 70 per cent, were under five years of age.

TABLE 2.

Mortality from Diphtheria in New York City
from 1891 to 1900.

Age	Number	Per cent.
Under 1 year	1,665	9.2
1-2 years	4,263	23.0
2-3 years	3,817	21.2
3-4 years	2,900	16.1
4-5 years	1,908	10.6
Under 5 years	14,553	81.5
5-10 years	3,052	17.0
10-15 years	241	1.3
Under 15 years	17,846	

TABLE 3.

Total Mortality and Mortality under Five Years
from Diphtheria in New York City
from 1901 to 1917.

Years	Total Mortality	Under 5 Years	Per Cent under 5 Years.
1901-1917	29,873	23,150	77.5

It will be seen, as Zingher⁽³⁾ remarks, from a study of these Tables 2 and 3, that children from 1 to 5 are most susceptible to the disease and show the greatest mortality. In one Table, 81.5 per cent of deaths, in another 77.5 per cent, are shown to have occurred under five years of age. He further remarked that the yearly mortality from diphtheria in the United States was 23,540 and the morbidity from the disease ten times higher, in spite of the very valuable therapeutic remedy in the form of antitoxin, and that it would therefore be of the greatest importance, considering these statistics, to utilize to the fullest extent a method of active immunization that would render the total infant population, as well as the susceptible portion of the child and adult population, protection against this disease. He considered that recent investigations into the subject of natural and active immunity in diphtheria and

studies with the Schick Test, a valuable clinical test which was now available for determining diphtheria immunity, would seem to offer a solution to the problem of the control of diphtheria.

EARLY WORK ON SUSCEPTIBILITY TO AND
IMMUNIZATION AGAINST DIPHTHERIA.

I. THE SCHICK⁽⁴⁾ TEST.

In 1908 an article appeared by Schick in which he describes a cutaneous reaction. Von Pirquet had established his tuberculin reaction and pointed out that it depended on a hypersensitiveness by previous injection of a foreign protein. Schick, who had assisted Von Pirquet in his work on Tuberculin, took up the question of diphtheria skin and conjunctival reactions, assuming that hypersensitiveness was developed in diphtheria. Schick's first problem was, did the human skin react to cutaneous injection of diphtheria toxin? Von Pirquet had injected diphtheria toxin with no result and Schick decided it was too dilute: he therefore concentrated it ten times and obtained a positive result. The reaction obtained resembled a tuberculin reaction. He took a patient

suffering from a mild faucial diphtheria and injected some dilute diphtheria toxin intracutaneously, and watched the reaction which followed for several days.

In 24 hours there was observed a dark red central area of inflammation 8 m.m. broad with a lighter area of redness surrounding this 20 m.m. broad.

In 48 hours the central area was dark red with a raised pustule in the centre of it, while the outer area was dull red in colour and itchy.

In 60 hours the pustule was still present.

In 72 hours the central area was still raised 9 m.m. broad, total area 30 x 20 m.m.

In 96 hours the central pustule was 11 x 8 m.m. broad: the surrounding redness had faded, and the pustule had dried. Pigmentation followed.

Schick considered that pustulation was part of the reaction and not due to accidental infection. He considered the reaction to be specific. He noted that it failed to appear if the toxin was neutralised in vitro by antitoxin and that it also failed to appear if the patient was passively immunized 24 hours previously with 1500-3000 units of antitoxin, and he formed these views from the following experiments. He took a patient with a mild faucial diphtheria and injected intracutaneously a drop of the following solutions:-

Sol.I. 1 c.c. toxin + 0.5 normal saline.

Sol.II. 1 c.c. toxin + 0.1 of 250 units serum +
0.4 normal saline.

Sol.III. 1 c.c. toxin + 0.4 of 250 units serum +
0.1 normal saline.

IV. Control.

He watched the results from day to day and noted that -

At 24 hours only a reddish scratch was visible where solutions I., II. and III. had been injected.

At 48 hours there was a papula 6 m.m. broad visible where Solution I. had been injected: the others were negative.

At 72 hours, the papula, visible at 48 hours, was 11 x 7 m.m. broad; the others were negative.

Fifteen hundred units of antitoxin were then injected subcutaneously into the patient, and he was again intracutaneously injected with a drop of solution I. When this was injected, there appeared at 24 hours a reddish scratch 3 m.m. broad, which disappeared entirely at 48 hours.

Schick concluded from his experiments that the injection of antitoxin weakened but did not suppress a previous Schick reaction, but it negated the one following. He stated that simultaneous antitoxin destroyed the reaction, but that antitoxin given a

few hours (1-4) after the Schick Test, had variable results, as out of seven cases, four were negative and three were positive: he thought that the positive reactions would have been stronger but for the antitoxin.

He injected another patient intracutaneously with different solutions containing toxin and varying amounts of antitoxin and observed that the toxic effect of a mixture of toxin-antitoxin was very little reduced in 24 hours; the action of the antitoxin only making itself felt at 48 hours and more so at 72 hours. The experiments showed that both the duration and intensity of the reaction was affected by the admixture of antitoxin (disappearance beginning at 48 hours), while, if pure unmixed toxin was used, the reaction remained maximal at 120 hours. Schick therefore thought that, since it took the antitoxin 48 hours to have its effect, the addition in vitro of antitoxin to the toxin was not itself sufficient to prevent the reaction, but that the tissues themselves played a third part - possibly by means of complement - and that, if there was sufficient of this material to hand, then the reaction was completely suppressed.

Schick gave 95 children intracutaneous injections of toxin: the children were all under 14 years of age

and not suffering from diphtheria.

TABLE 4.

	Total	Pos.	Neg.	Per cent. Pos.
Infants under 1 Year	21	1	20	4.7
1-3 Years	5	2	3	40.
3-5 Years	13	9	4	69.2
5-7 Years	18	10	8	55.5
7-10 Years	20	7	13	35.
10 Years	18	7	11	38.8

Table 4 shows the numbers of positives and negatives found by Schick at different ages in doing some of his tests. He also gave intracutaneous injections to 22 children with diphtheria and not treated with antitoxin, and found that 18 of these gave positive reactions to diphtheria toxin, that 3 were doubtful, and that 1 was negative.

Using a stronger toxin, Schick got the following results, viz. 31 out of 33 infants gave a positive reaction, though the reactions were milder than usual; 31 children, from 1-14, gave 29 positive reactions with the same toxin. Schick concluded that the reaction was not purely an anaphylactic phenomenon since, with a solution of increased toxicity, positive results were obtained even in healthy people. He

thought that the findings could be interpreted in another way, based on the fact that Wasserman had shown that with increasing age antitoxic substances to diphtheria increased in the blood: and so Schick deduced that the different reactions obtained were with a difference of the antitoxin content of the blood; a positive result being caused by an absence of antitoxin. The cutaneous reaction was therefore a measure of individual susceptibility to diphtheria. This agreed with his findings that the intensity of the reaction between 3-7 years was greater than at any other period and arose from the small amount of antitoxin in the blood. Statistics had shown that 3-5 years had the greatest case incidence of diphtheria. Schick concluded by suggesting that test was of little value for diagnosis (as opposed to tuberculin) but that it afforded a new method of studying toxin-antitoxin processes. He hoped that it would be possible on the basis of the Schick reaction to build up an exact dosage of antitoxic serum.

In November 1913 another article by Schick⁽⁵⁾ appeared. He declared that children suffering from diphtheria had no antibodies in their blood, but that the prophylactic injection of antitoxin into persons exposed to infection made up for the absence of such

antibodies. He stated that there were numerous individuals who without ever showing symptoms of diphtheria nevertheless had antibodies against diphtheria toxin in their tissues, i.e., newly born infants - over 80 per cent. - adult, a large number, and a considerable percentage of children. He thought that it would be possible to spare a large number of persons an injection of prophylactic serum if we had a simple method of showing such people as had antitoxin already in their blood. He considered the older methods, such as the injections of guinea pigs to be too cumbersome, and gave a description of the method of intracuraneous injection of diphtheria toxin in human beings. He proved that a negative reaction always indicated the presence of protective substances against diphtheria toxin in sufficient concentration to act as a prophylactic except in a few exceptions - some newly born infants, etc. A positive reaction did not indicate with equal certainty the absence of protective bodies, he thought, since many individuals - children and especially adults - gave inflammatory reactions in spite of the presence of antibodies in their serum. These reactions were not specific to diphtheria toxin, but were probably due to protein hypersensitiveness. Definite conclusions could only be drawn, therefore, he thought, from negative

reactions. Assuming the presence of antibodies in the serum to be incompatible with an attack of diphtheria, we could deduce that children suffering from diphtheria always gave a positive skin reaction. In practice he found this to be true. In doubtful cases therefore, a negative reaction excluded diphtheria. He noted that of all nurses who were schicked in his clinic, only those who gave a positive reaction took diphtheria.

He went on to say that he was sure that the skin test showed the measure of susceptibility to diphtheria.

TABLE 5.

Schick (1913).

	Total	Pos.	Neg.	Per cent. Neg.
Newly born	291	16	275	93
1st Year	42	18	24	57
2-5 Years	150	95	55	37
5-15 Years	264	131	133	50

For the test to be of use in diminishing the number of injections of serum given prophylactically, we must have proof, said Schick, that the percentage of negatively reacting persons was sufficiently large, and as an indication of this he quotes the figures in

Table 5 by Magyar and Schick. Schick considered that in the newly born infants a prophylactic dose of serum in the vast majority of cases was unnecessary and this corresponded with the findings in various orphanages, i.e., newly born children very rarely took diphtheria when exposed to the usual sources of infection. Even at the time when diphtheria was most frequent, i.e. from 2-5, there were still a number of persons for whom a prophylactic injection was unnecessary. The objection might be raised, thought Schick, that the level of immunity of a given individual was not fixed and that illness (influenza, measles) might influence unfavourably the protective power of the body. As far as his experience went, the reaction in healthy children had remained constant for weeks, but repeated testing would prove this. For such institutions as Hospitals, Barracks, Boarding Schools, etc., the test, he thought, was of practical value. Schick's system was as follows:- If a case of diphtheria occurred, every one was at once tested with the skin test: after 24 hours we had an indication of the result. Positive cases were immunized; negative cases were left alone. In this way a large number escaped injections of serum with its consequent risk of producing anaphylaxis, and in addition there was a considerable economy in

the drug bills of the institution.

The amount of toxin injected in doing the test as recommended by Schick was 1/50th M.L.D. for the guinea pig in normal saline. He estimated that a negative Schick indicated at least 1/30th of a unit of antitoxin per cubic centimetre of blood - enough to protect against diphtheria.

II. TOXIN ANTITOXIN MIXTURES - VON BEHRING⁽⁶⁾.

In 1913 Von Behring made announcements with regard to a bacterial emulsion which he had devised with the object of producing immunity to diphtheria lasting several months. More than one injection was necessary and the active protecting bodies were produced from three to five weeks after inoculation. The product was an emulsion of virulent diphtheria toxin with antitoxin in such proportions that the mixture was innocuous to the guinea pig. Behring found that mixtures non toxic for guinea pigs might in the monkey and ass produce marked febrile reactions with the formation of antitoxin in large quantities. The reaction in man was less violent, but varied considerably with age, being least marked in infants. Carriers, and those whose blood reaction, as expressed in units of antitoxin, proved them to

have been carriers of bacilli at some time, were found to be hypersensitive to the mixture and very readily produced large quantities of antitoxin after injection.

Behring quoted a case from Marburg in which 600,000 units of antitoxin had been produced where 250 units would have ensured to ensure immunity. This case was only injected with $\frac{1}{16}$ c.cm. of toxin-antitoxin emulsion and was noteworthy, for a second child was for the first time passively immunized from it, i.e., it was immunized with an anthropogeneous or homogeneous, as opposed to a heterogeneous serum, and it was found that the immunity thus obtained was of far longer duration than could be obtained with horse serum antitoxin. This was a discovery of great importance by Von Behring, for not only was the immune period prolonged, but the risk of anaphylaxis was eliminated.

Behring at once stated that he was ready to put his emulsion, as he called it, on the market for the purpose of finding out from clinicians the ideal dose which might produce a minimal local and febrile reaction with a maximum of antitoxin production. Behring recommended the use of the mixture (1) among diphtheria carriers to determine the destruction of nasopharyngeal bacilli as rapidly as possible; (2)

to manufacture a prolonged immunity; and (3) for the manufacture from highly immunized subjects of an anthropogeneous serum, both for passive immunization purposes and for the cure of the actual disease.

Schreiber made an announcement concerning the mixture of toxin-antitoxin in the same journal. He stated that the remedy was harmless and fully capable of producing immunity. Behring received a communication from the surgical side of his institution that no inoculated children had been infected, or could be reported to be carriers up to the time of his making his report, although an epidemic of diphtheria was raging in the wards at the time.

In the later number of the same paper, Professor Zangemeister stated that it was important to establish immunity as rapidly as possible after birth, and that inoculation of infants was not only possible but advisable because the reactions in them were less violent than at later ages, and were constant. Von Behring estimated that the adult was about one hundred times more susceptible to the mixture of toxin and antitoxin than the infant, and he was of opinion that this hypersensibility rested solely on a preceding infection in the case of the former, an infection which probably had run its course without producing any of the classical symptoms of the disease.

Von Behring⁽⁷⁾ reported in 1914 the results obtained since the injections were commenced a year previously. In a number of cases injected, he continued to estimate the antitoxin content of the serum at regular intervals and found that though the amount present was a gradually diminishing quantity, more than sufficient still remained to protect the individual against the disease during an epidemic. He made the discovery that amongst controls who had never had a single injection of antitoxin, there existed individuals whose blood contained an auto-genous antitoxin against the disease, and that in infants the number of the immune amounted, according to blood estimation, to between 60 and 80 per cent. Adults were found also to contain a high content of natural antitoxin, but school children, in whom the morbidity from the disease was high, were estimated by laboratory tests to be singularly deficient in antitoxin. During the previous year, Von Behring stated, 1000 cases were injected with the mixture of toxin-antitoxin in many clinics and institutions, and regular examinations of the antitoxin content of the serums were carried out, together with control examinations for Klebs-Loeffler bacillus in each case. Besides these, over 2000 cases were injected without this control, and Von Behring considered - 1914 -

that he was justified in claiming that the prophylactic potency of the new product was fully equal to that of vaccine in smallpox prevention.

Emphasis was laid on the fact that among 7000 injections given, there had been no unpleasant sequelae - a result which he attributed to the careful control of each specimen sent out by previous animal inoculation. Intracutaneous injections he considered the best, and two of these at an interval of not less than ten days were amply sufficient in the large number of cases to ensure a satisfactory protection.

Von Behring declared that sufficient protection against diphtheria exists when 1/100th of a unit of antitoxin was present in every cubic centimetre of blood.

SUBSEQUENT WORK IN CONNECTION WITH THE SCHICK
TEST AND TOXIN - ANTITOXIN IMMUNIZATION.

Since Schick and Von Behring first described their methods, much work has been done on this whole subject, especially in America, by Park and Zingher, and in this country by O'Brien, Eagleton, Glenny, Allen, etc., as well as by Blum, Moody, Bundesen, Leete, Ward, Dickinson, Dudley, and many others.

A very full Bibliography is given in the Monograph on Diphtheria by the Medical Research Council - H.M. Stationery Office, 1923. Leete⁽⁸⁾ was the first in this country to publish clinical observations on the Schick Test - work done in the Edinburgh City Hospital - while some of the earliest work with the Schick Test and with immunization by means of toxin-anti-toxin mixtures in this country, was carried out by O'Brien⁽⁹⁾ and his co-workers.

TECHNIQUE OF THE SCHICK REACTION.

As is well known, the Schick Test consists in the intradermic injection of .2 c.cm. of a diluted diphtheria toxin; the .2 c.cm. containing 1/50th of a minimal lethal dose for a guinea pig. The toxin which we have used at the Edinburgh City Hospital during the last two years in the carrying out of about 7000 tests (including controls and retests) was prepared by Dr O'Brien and supplied from the laboratory of Messrs Burroughs and Wellcome. The dose has been 1/50th of a M.L.D. for a guinea pig (as already stated above). The .2 c.cm. of diluted toxin is injected into the skin of the left forearm just below the bend of the elbow, while .2 c.c. of

heated toxin of a similar dilution is injected into the skin of the right forearm to act as a control. The control solution heated to 75° C. for ten minutes loses its toxin action but still retains the proteins to which the pseudo reaction is due.

It is absolutely necessary to have an all glass 1 c.c. syringe of the "Alga" type, as supplied by Messrs Burroughs and Wellcome. The blue 1 c.c. Tuberculin syringe is a beautiful fit and during the injection of the toxin allows no leak back between the barrel and the piston, so ensuring that exactly .2 c.cm. is injected. The small dental needle - about half an inch long and also supplied by Messrs Burroughs Wellcome - is very suitable; it should be sharp. It is very important that the dosage should be accurate, especially if a control test is being done, and especially so in the adult, as it is the adult who gives the pseudo reaction which is such a disturbing factor and may lead to much confusion.

The injection must be intracutaneous, and, when done correctly, a raised white wheel is produced. It is unnecessary to go into detail as regards the reaction which follows. The papers of Leete, Glenny, Allen and O'Brien, and Ward⁽¹⁰⁾ give this in detail. Children, who seldom show a pseudo reaction, give no trouble as a rule when the readings are made, but

adults may be very difficult and almost impossible to read correctly, especially if they have had diphtheria and antidiphtheretic or other serum, or have been in contact with diphtheria for years and have thus become carriers and so perhaps sensitized to protein.

The clear-cut negative and positive reactions without a pseudo reaction are easily read, but the combined positive and pseudo, and the combined negative and pseudo reactions are often extraordinarily difficult to estimate. The pseudo reaction usually comes up before the true reaction and usually fades much more rapidly, so that by the fourth day after making the test there should be little difficulty in saying whether the individual is positive or negative - more especially if a confirmatory reading is made on the tenth day. Sometimes, however, there is a considerable amount of bluish pigmentation with desquamation in both arms, and it is extremely difficult to say whether the reading is negative or positive.

Fortunately it is seldom necessary to Schick Test adults unless they are nurses in hospital, and, when in doubt, it is usually wise to call the reaction a positive one and to give the immunising mixture, even though such an individual will in all likelihood suffer from a fairly severe local and constitutional disturbance about 24 hours after receiving

the toxin-antitoxin.

It is never necessary to boil the syringes - of which there should always be two, with one suitably marked so that there is always one syringe for the right arm and another for the left arm. In doing all the tests, in the City Hospital, the syringes were never boiled, but before beginning the tests each syringe was washed out with methylated spirit and ether and allowed to dry before use, while the needle point was just wiped on a pledget of cotton wool soaked in spirit between each test. The arm was always cleaned up with a little cotton wool soaked in ether, which is better for the purpose than alcohol, as it dries up quickly and leaves the skin nicely prepared for the injection.

With this technique, no septic inflammation occurred in about 7000 injections given. We have used the same needle and the same syringe continuously for some weeks while doing hundreds of tests. This technique saves time when there are hundreds of children to do at a time, and so it is possible for two workers to test about 300 children comfortably in an hour, with good organisation. It is not wise to make the injection too hurriedly, as a subcutaneous instead of an intracutaneous injection might give an entirely false reading, with disastrous consequences,

a child who was really a positive being called a negative reactor.

TABLE 6.

Total Cases (Sept. 1922 to Sept. 1924),
City Hospital, Edinburgh.

Age Period in Years	Total	Negative	Positive	Per cent. Positive
0- $\frac{1}{2}$	21	16	5	23.8
$\frac{1}{2}$ -1	61	15	46	75.4
1-2	197	39	158	80.0
2-3	234	36	198	84.6
3-4	294	81	213	72.4
4-5	244	62	182	74.5
5-10	841	331	510	61.8
10-15	410	194	216	52.6
15-20	310	140	170	54.8
20-30	557	234	323	57.9
30-40	100	53	47	47.0
40-50	27	12	15	55.5
50-	15	11	4	26.6
Totals	3,311	1,224	2,087	63.0

This Table (6) includes all individuals tested - patients suffering from scarlet fever, measles, whooping cough, surgical tuberculosis, erysipelas, enteric, chickenpox, puerperal fever, meningitis, encephalitis lethargica, etc.; all the hospital nurses, maids of the domestic staff, students, resident medical officers, and children of the staff. The table originally appeared in a paper in the Lancet by Dr Ker⁽¹¹⁾ and

myself, in May of this year, and consisted of 2176 cases: to this I have added 1135 cases, consisting mainly of scarlet fever, measles and whooping cough patients, with a few others, for the testing of which I have been responsible. It is interesting to note that the addition of over 1000 cases to the previous table has altered it so slightly. Table 6 shows that the age of greatest susceptibility to diphtheria as shown by the Schick Test is between 2 and 3, the figures being 84.6 per cent. as compared with 82.9 per cent. in our previous table. The age period 0-6 months gives still a low figure, 23.8 per cent. of positives, showing that at this age there is a natural immunity. The age period from 6 months to 1 year gives in Table 6 a positive percentage of 75.4 as compared with a percentage of 75. in the former table. The age period 10-15, 15-20 and 20-30 would probably have been lower in this table than in our previous one but for the fact that these age periods include an extra number of public school boys and highland nurses and maidservants, who practically all gave a positive reaction, showing that they had not acquired an immunity because they had not been in contact with as much infection as they would have been if they had attended school or had lived during childhood in the poorer parts of our great cities. It is

interesting to note that whereas the total positive percentage figure was 61.2 in our previous table, in table 6 the figure is 63.0.

The table shows the gradual decline of susceptibility with increasing age, after its initial rise to the period of greatest susceptibility between 2 and 3 years. With a little calculation Table 6 shows that in just over 1000 children tested - from 6 months to 5 years - 77 out of every hundred are susceptible to diphtheria as estimated by the Schick Test, an interesting figure when one remembers that 70 per cent. of the total deaths from diphtheria last year in Edinburgh were under 5 years of age.

The figure is also interesting when one recalls Table 3 which showed that between 1901 and 1917, 29,873 people died of diphtheria in New York City, and that 77.5 per cent. of these were under five years of age.

TABLE 7.

Percentage of Positive Tests in Scarlet Fever,
Measles and Whooping Cough, City Hospital.

Age Period in Years	Scarlet Fever		Measles		Whooping Cough	
	Number Tested	Per Cent. Pos.	Number Tested	Per Cent. Pos.	Number Tested	Per Cent. Pos.
0- $\frac{1}{2}$	4	25.0	4	25.0	10	30.0
$\frac{1}{2}$ -1	11	81.8	29	79.3	19	63.1
1-2	41	82.9	107	82.2	47	72.3
2-3	122	85.2	66	89.3	41	75.6
3-4	178	76.4	73	71.2	38	55.2
4-5	168	80.9	45	62.2	20	65.0
5-10	714	62.3	72	58.3	31	38.7
10-15	374	50.5	14	78.5	3	33.3
15-20	125	44.8	20	75.0	-	-
20-30	105	38.3	19	78.8	-	-
30-40	48	45.8	2	100.	-	-
40-50	20	55.0	-	-	-	-
Totals	1912	62.2	451	74.5	209	60.7

Table 7 can be compared with the similar table in our previous paper. To that table I have added 714 cases of scarlet fever, 287 cases of measles, and 75 cases of whooping cough, the result being Table 7 which shows the susceptibility rates of the scarlet fever, measles and whooping cough cases. Dr Ker remarks, with regard to the former table, that the total percentage of positive scarlets was high, though the figure 62.1 was not very different from the figures found in the same wards in 1920 and 1921 by Leete and

Ward, 57 and 56 respectively, whereas Zingher⁽¹²⁾ had shown only 45 per cent. of positives out of 1200 cases of scarlet fever in New York, and Dickinson⁽¹³⁾ had shown only 47.4 per cent. in Manchester. Table 7 shows that though 714 scarlet cases have been added to our previous table, yet the positive percentage is 62.2 - being actually .1 more than previously - for a total of 1912 scarlet cases.

Scarlet fever cases are undoubtedly unduly susceptible to diphtheria and Zingher considered his figure a high one when compared with the susceptibility of normal children. Zingher⁽¹⁴⁾ considered that this susceptibility might be due to a destruction of natural antitoxin during an attack of scarlet fever. Zingher's views on this point have somewhat changed, as in a communication received from him recently, he says that he was wrong in formerly considering certain groups of children normal with a fairly low Schick positive percentage. These so-called normal children were really children from a poor class who had lived long among likely infection with diphtheria and had developed some immunity, as compared with groups of children and even students who, living in better social surroundings, gave a much higher Schick positive percentage. The reason why the positive percentage is high he considers

rather to be due to the fact that many of his scarlet fever patients belonged to the better classes, and the undue susceptibility of scarlet fever patients to diphtheria he now considers rather due to the local condition of the nose and throat which is ready to receive infection as a result of the scarlet and not to any reduction of the antitoxin content of the blood due to that disease. The character of the population from which the scarlet fever cases come probably explains why in Table 7 there is a high rate of susceptibility to diphtheria, because 95 per cent. of all cases of scarlet fever are treated in hospital in Edinburgh and a great many of the children are country children who come in to Edinburgh to school, not to speak of the students and others whose homes are really in the country and who all help to raise the susceptibility rate. This point is well borne out in looking at the measles rate of susceptibility in Table 7, and especially at the age groups 10-15, 15-20 and 20-30. The average positive percentage of these age groups is over 75 and is entirely due in the first two age groups to the fact that there was a small epidemic of measles in two well known public schools in Edinburgh, i.e. Edinburgh Academy and Fettes College, and these figures really represent individuals who were all susceptible to diphtheria

coming from homes and schools where they had had little chance of picking up an immunity. Zingher⁽¹⁵⁾ has shown that the children in the poorer class schools in New York have a much lower susceptibility rate than those from good class schools. The age group 20-30 consisted of Highland students, maid servants and policemen. It is a well known fact that people from the highlands very often escape measles and other infectious diseases till they come into large towns and cities, and this is borne out in this group actually suffering from measles and showing by means of the Schick Test a susceptibility rate of 78.8 per cent. to diphtheria as well.

The whooping cough figures in Table 7 are interesting by comparison, as instead of a susceptibility rate of 58.3 for the age group 5-10 in the case of measles, the susceptibility for the same age group in the case of whooping cough is only 38.7, this low figure being due, we think, to the class from which the children were drawn. All over, the susceptibility rate in whooping cough as shown in Table 7 is lower than that of either measles or scarlet fever, probably for the same reason.

Dr Ker and I show a table in our paper consisting of a group of students with a positive percentage rate of 61.7; a group of nurses with a positive percentage

rate of 64.7; and a group of maids with a positive rate of only 38.1. This high rate of susceptibility in the first two groups can be explained from the fact that the students and nurses come from good class homes, and many from the country, and agrees with Dr O'Brien's⁽¹⁶⁾ figures, namely, 65 per cent. in a group of medical students.

It is interesting to note the low susceptibility rate of the maids as compared with the students and nurses.

TABLE 8.

Pseudo Reactions: 2176 Tests.

Age Period in Years	Per Cent. of Pseudo Reactions.	Per Cent. of Positive Schicks.
0-5	0.86	74.6
5-10	3.1	58.4
10-15	7.6	52.0
15-20	26.7	53.5
20-30	31.4	59.3
30-40	32.8	48.6
40-50	38.8	44.4
50-	41.6	25.0
Totals	13.0	61.2

This Table (8) is taken from the paper by Dr Ker and myself - work done in the City Hospital, Edinburgh - and shows the pseudo reaction rate as contrasted

with the susceptibility rate to diphtheria for the same age groups. All these tests were read on three successive days after the injection, and again on the tenth day for the purpose of finding out the most suitable day on which to estimate the Schick reaction, and we came to the conclusion that the fourth day and the tenth day were the best, if two readings were to be done: the fourth day was suitable because by that time, as far as children were concerned, there was practically no difficulty with the pseudo reaction which is at its height before 48 hours and has practically gone by the fourth day in the majority of cases - except in those adults who are hypersensitive to protein. The eighth day we considered most suitable if only one reading is to be done, because on that day - a week after being given the testing injection - children in a school could both have the arms read and receive their first immunising dose of toxin antitoxin mixture. It should be noted from a study of Table 8 that under five years of age the protein susceptibility rate is practically negligible as compared with the susceptibility rate to diphtheria, while under ten years of age the protein susceptibility rate is so slight that it can be discounted when considering immunization of children of that age period, and so we were able to advise the Edinburgh

Public Health authorities that the control test could be dispensed with and the amount of work lessened - at least as far as the first Schick test was concerned - when testing the numbers susceptible and likely to require immunizing.

Table 8 shows the rise in protein susceptibility rate as age increases, that is to say, the individual as he grows older becomes more susceptible to protein, while at the same time he becomes less susceptible to diphtheria. It is a point of great practical importance that we should have so few pseudo reactions among children under five years of age, as this, being the age period of the greatest susceptibility to and mortality from diphtheria, is the time when these children require to be protected with immunizing doses of toxin-antitoxin. In the course of giving 2500 injections of toxin-antitoxin to children under ten years of age, I have not noticed a single severe local or general reaction in any child after receiving full doses of the mixture. Older children, but especially adults who show a very much larger number of pseudo reactions, may suffer considerable reactions both locally and generally. It is fortunate that adults as a rule do not require to be immunized, with the exception of hospital nurses in infectious diseases hospitals.

In over 1000 tests performed since Table 8 was published, I have observed pseudo reactions in only 7 cases, and 5 of these pseudo reactions occurred in individuals over 10 years of age. The explanation of this very low rate of protein susceptibility is that the readings were done on the fourth day and not at 24, 48 and 72 hours as in the 2176 tests in Table 8. In the case of the two pseudo reactions observed under 10 years of age, one of these would not have been noticed but for the fact that the arms were read in this particular individual at an earlier date for another reason; the fourth day reading showed no sign of a pseudo reaction.

The control test therefore is quite useless unless the readings are done before the fourth day. Lately I have read the tests in the case of the nurses at 48 hours, 4 days and 10 days after the Schick test was done, and I consider these to be very suitable days if a true reading of the test and control is desired in the adult.

INCIDENCE OF DIPHTHERIA IN POSITIVE AND
NEGATIVE SCHICK REACTIONS.

During the last two years' work there have occurred 39 cases of diphtheria among those who had

been tested, and of these 33 gave positive reactions, including one maid and four of our own nurses, while 6 were thought to be negative. Of these 6 cases, one was negative because of the previous injection of a small prophylactic dose of antitoxin and later developed diphtheria when this passive immunity had passed off; and one, read as a negative reaction without any pseudo phenomenon, subsequently developed a good clinical diphtheria followed by a palatal paresis. This was the only child in hospital out of over 770 negative schick reactions, under fifteen years of age, who developed diphtheria during the whole of the two years' work, though many of those were exposed daily to infection.

The other four negative reactions were our own nurses. Two of the four were noted as negative when Schicked on arrival at the hospital for duty, and the other two were also thought to be negative after receiving immunizing doses of toxin-antitoxin. It will be interesting to discuss these four nurses in detail.

One, Nurse S., was schick tested on 18/9/23 and showed on the third day a reaction so slight as to be almost negligible (which I shall designate \pm) on the right or control arm, and a small positive reaction, (designated \oplus), on the left or test arm. The tenth day reading showed apparently nil in the way of

pigmentation or desquamation on either arm, and was read as a negative reaction without a pseudo. This nurse on 4/6/24 developed a tiny patch, about the size of a threepenny piece or less, on the left tonsil, with just a speck on the right one. She was warded and reschicked. While waiting 24 hours for the schick reaction to declare itself, the throat cleaned up completely and no antitoxin was administered, but she was treated otherwise as a mild case of diphtheria. The swab was positive, while the schick reaction gave a marked reaction on both arms, but as the right arm reaction had faded considerably by the third day, while the left arm reaction faded less quickly and later showed slightly more pigmentation, the conclusion was that the reading was a positive one with a combined pseudo reaction.

Nurse H. was schicked on 25/4/24 on arrival at the hospital and noted as negative reactor, without a pseudo reaction. On 10/8/24 she complained of sore throat and examination of the throat revealed some scumminess on both tonsils, which were red and enlarged. The swab was positive on the first occasion, but negative on subsequent days. The throat was long in clearing up and was more suggestive of a slightly septic throat than of a diphtheritic infection. She was reschicked on admission to the ward.

The schick reaction was not easy to estimate, as there was a marked reaction on both arms, always, however, slightly larger on the left than on the right, and on the tenth day showing a very faint pigmentation in both arms, but slightly more evident on the left than on the right one. She was noted as a faint positive reactor, with a pseudo reaction, i.e. a combined positive and pseudo. She was given a small amount of antitoxin 24 hours after being schicked and treated as a mild diphtheria.

The following two nurses, who had been originally schick positive, had received immunizing doses of toxin-antitoxin and on reschicking were noted as negative.

Nurse B. was first schicked on 5/9/22, when she was noted as a schick positive reactor, without a pseudo reaction. She was therefore immunized with three doses of toxin-antitoxin, the immunization being completed on 16/11/22. She was reschicked at three and six months after immunization and noted as a negative without a pseudo reaction on each occasion. On 30/5/23 she was warded with scummy patching on both tonsils which suggested diphtheria, but quite well might have been just a septic condition, as the throat took some time to clear up: the swab was positive. She was not schicked on admission to the ward. She

was given a moderate dose of antitoxin and treated as a mild case of diphtheria.

Nurse I. on 5/9/22 showed a positive schick reaction without a pseudo phenomenon. She was consequently immunized with three doses of toxin-antitoxin. The immunization was completed on 10/11/22. On being reschicked three months later, she was still positive, but three months later still she was noted as a combined negative and pseudo reactor. The third day reading, however, showed more on the left arm than on the right one. On 13/2/24 she was warded with a slight patching on both tonsils, which was suggestive of diphtheria: the swab was positive. She was reschicked on admission to the ward and a reasonable time afterwards she was treated with a moderate amount of antitoxin. The schick reaction was noted to be a slightly positive one, with a pseudo reaction. She was treated subsequently as a mild case of diphtheria.

These cases show the difficulties which are met with, particularly in properly estimating a real positive and negative Schick reactor in the case of the adult with a pseudo reaction.

The following case shows how the absence of the pseudo reaction makes the reading of the Schick test much easier.

A child, W.B., was admitted to a scarlet fever

ward suffering from an attack of scarlet fever. The tonsils were scummy and the type of case suggested a mild septic scarlet. The child on admission was given the Schick test and was noted at 24 and 48 hours as a negative reactor, without a pseudo reaction. At this time the throat was more suggestive of diphtheria than on admission, as, in addition to scummy patching on the tonsils, there was involvement of the uvula, which was well covered with a whitish scummy patching. A swab revealed a large number of organisms morphologically indistinguishable from the diphtheria bacillus: curiously enough, although the first swab was positive, the subsequent swabs were completely negative. The child was reschicked, and again gave an absolutely definite negative reaction without a pseudo reaction. As a precaution a moderate dose of antitoxin was administered. The throat condition cleared up very slowly and behaved in every way like a septic throat: there was still some smooth looking patching on the uvula a week later: this gradually disappeared. This case was subsequently treated as a scarlet alone, and not as a diphtheria one.

TABLE 9.

Percentage of Positive Tests
in the Nurses of the City Hospital.

Age in Years	Number	Negative	Positive	Percentage Positive
15-20	112	36	76	67.8
20-30	105	36	69	65.7
30-40	6	4	2	33.3
40-50	0	-	-	-
50-	2	1	1	50.
Totals	225	77	148	65.7

Table 9 was originally part of a combined table in the paper on the Schick Test by Dr Ker and myself. I have added to it a number of nurses - 29 -, and it will be seen that the addition of this number has not altered the diphtheria susceptibility rate of the total number, which is 65.7 in this table compared with 64.7 in our previous table.

The susceptibility rate is undoubtedly high but, as pointed out previously, most of our nurses are from the country and from good class homes as compared with the maids.

The fall of susceptibility with increasing age is shown, even though the numbers in the highest age group are too few. The percentage of pseudo reactions is 33.3 for all the nurses tested, while it is

over 40 per cent. for the Schick positive nurses alone, thus showing a higher pseudo rate than for the Schick negative reactors. This is contrary to what is usually found, for instance, by Zingher⁽¹⁷⁾ and by Dudley⁽¹⁸⁾, who found the pseudo rate higher among immunes than among non-immunes, and contrary to what we found ourselves in a group of students attending the fever clinic at the City Hospital. In this group of 245 students, there was a percentage of pseudo reactors of over 32 for all the students tested, but the pseudo rate for the 155 positive Schick reactors was 27 per cent. as compared with a pseudo rate of over 41 per cent. for the 90 negative Schick reactors. The reason for the high pseudo rate among the non-immune nurses is probably that so many of these nurses giving as they did still a high diphtheria susceptibility rate - 65.7 - developed diphtheria early in their stay in hospital and received antitoxin. They were thus sensitized to protein but were still susceptible to diphtheria. As is well known, one attack of diphtheria does not confer immunity; for instance in a group of 194 patients who gave a history of having had diphtheria previously, 48.8 per cent. were found by us to be positive Schick reactors.

Other nurses who did not develop diphtheria, probably became sensitized to protein by receiving small

non-infecting doses of diphtheria from close contact with the disease, and remained susceptible to the disease, as shown by the Schick test later. In some later tables I have grouped the nurses whom I immunized into two lots. In the first group are placed roughly all the nurses who had been in hospital for a considerable time before being Schick tested - even up to two and three years - and during that time constantly exposed to all kinds of infectious diseases, and in the second group are placed all the nurses who were Schick tested immediately on arrival in the hospital or very shortly after arrival.

In the first group the pseudo rate for these positive reactors was 46.5 per cent., and in the second group, 28 per cent. How these two groups reacted to toxin-antitoxin mixtures will be shown later. As a contrast to these two groups of adults with different pseudo susceptibility rates might be noted a group of Schick positive children - 312 in number - whom I also immunized in the City Hospital. The pseudo rate in this case was only 1.6 per cent., but this is not an accurate interpretation of the pseudo rate of this group, because in so many of them the reading was done on the fourth day, when the pseudo reaction, if present, would probably have disappeared. All except 25 of these 312 children were under 10 years of age,

and reference to the table of pseudo reactions and a little calculation will show that the average pseudo rate from 0-15 is 3.85 per cent, representing the number of children of that age period tested, i.e. 1384, so that the pseudo rate for this third group of 312 children would probably not exceed a similar figure.

TOXIN-ANTITOXIN MIXTURES.

A passive immunity can be produced by means of anti diphtheretic serum, but this immunity, which develops in about 24 hours, lasts only about 21 days. An active immunity which lasts for years, and may be for life, can be produced by means of a mixture of toxin and antitoxin. The power of toxin-antitoxin mixtures to produce immunity in animals has been long known. Park⁽¹⁹⁾ and Zingher, reporting their early work with toxin-antitoxin mixtures, claimed to have produced immunity in animals in 1903.

Although Theobald Smith is said to have been the first to suggest that antitoxin mixtures should be used to immunize children, Von Behring - as previously indicated - was the first to make the attempt. Many observers reported results, but Park and Zingher have published by far the largest amount of work done with

toxin-antitoxin mixtures in the immunization of many thousands of children in New York. The mixtures as used by Behring were either neutral or slightly toxic to the guinea pig, and individuals were injected with small doses and the injections repeated in from seven to ten days. The injections were at first - i.e. Von Behring - given subcutaneously or intramuscularly, but later he gave them intracutaneously as the more distinct local reaction was supposed to induce greater immunity.

When Park and Zingher began the use of toxin-antitoxin, mixtures were used which were either slightly antitoxic, neutral or slightly toxic to the guinea pig. A strong diphtheria toxin was used where the minimum lethal dose was 0.0023 c.c. and the L + dose 0.27 c.c.

The minimal lethal dose of a toxin (or filtrate) is the amount of toxin which will kill standard guinea pigs of about 250 grams weight in about four days.

The L + dose (or test dose) of a toxin is the amount which, when mixed with a unit of antitoxin and injected into a 250 gram guinea pig, will cause its death at the end of four days.

Park and Zingher's mixtures represented 50 per cent., 66 per cent., 80 per cent. and 90 per cent. of the L + dose of toxin to each unit of antitoxin, and

they found that 1 c.c. of the last named mixture when injected into a guinea pig caused at first a slight local induration and, in about 20 days, paralysis. The doses given by Park and Zingher to individuals for the purpose of producing immunity were given subcutaneously or intramuscularly, in doses of from 0.25 to 1 c.c., and the dose was repeated at intervals of from three to seven days. The local reactions consisted of varying degrees of redness, induration, pain, and tenderness, depending partly on the size of the dose and the individual susceptibility. The constitutional symptoms were as a rule mild: occasional temperature reactions of from 1 to 3 degrees were noted after larger doses.

The results of active immunization were controlled by finding out the antitoxin content of the blood both before and after the injections. Park and Zingher found as a result of their work that active immunization produced a very decided increase of antitoxin in a relatively short time in all persons who had natural antitoxin, and they stated that, in a series of 700 scarlet fever patients tested for natural immunity by the Schick reaction, 300 were Schick positive and were immunized. In about three weeks time they were again tested and less than a quarter of the number immunized with toxin-antitoxin

mixtures showed active immunization to a degree sufficient to immunize them: a larger percentage developed a trace of antitoxin. Although the immediate results were disappointing, yet it was hoped that the later results might prove more successful when the same individuals were retested at a later date. The slow development of immunity in the case of guinea pigs when injected with toxin or with toxin-antitoxin was well known and formed the basis for the hope that a sufficient immunity would develop in man, even though it was somewhat tardy. Later figures showed this to be so.

Zingher⁽²⁰⁾ later (1918), after further work on the subject, recommended that toxin-antitoxin mixtures used for immunization should be slightly toxic and should represent about 85 per cent. of an L + dose of toxin to each unit of antitoxin. The mixture should be prepared with a diphtheria toxin of such strength that each dose of 1 c.c. of the mixture will contain at least three almost neutralised L + doses of toxin. Various mixtures were used by Zingher⁽²¹⁾ as time went on, and in 1921, in immunizing school children, he sometimes used mixtures representing 3 L + doses of toxin to 3.5 units of antitoxin, and at other times 5 L + doses of toxin and a corresponding amount of antitoxin. He, at one stage, in immunizing a number of schools, gave only two doses of toxin-antitoxin

of 1.5 c.c. each, and this was done to simplify the work in the schools. He came to the conclusion, however, that better results were got by giving three doses of 1 c.c. each.

After extensive work in active immunization carried on for three years in schools and health stations in New York, Zingher⁽²²⁾, speaking at the Annual Meeting of the Medical Society at New York City in May 1923, said that certain observations which they had been able to make had led to certain conclusions as to the type of toxin-antitoxin which it would be best to use if protection against diphtheria was to be generally adopted. He said that until quite recently they had used - as already shown - quite extensively mixtures of toxin-antitoxin that contained 3 to 6 L + doses of toxin per c.c. They contained large amounts of different proteins which gave rise to disagreeable local and constitutional symptoms, chief among these substances being the autolysed protein of the diphtheria bacillus contained in the diphtheria toxin broth culture. Zingher found, using mixtures with 3 and 6 L + doses per c.c., that the mixtures containing the larger number of L + doses were not more efficient than those with the smaller number of L + doses, as long as the mixtures were equally toxic, i.e. equally under neutralised with

antitoxin. In fact, mixtures with a smaller number of L + doses per c.c. but showing greater toxicity for the guinea pig, gave better immunizing results than those with the larger number which were more neutralised. Dr Park therefore had mixtures prepared by Dr Banzhaf containing only a fraction of an L + dose of toxin per c.c. but so balanced that the under-neutralised fraction of the toxin-antitoxin was the same as that of mixtures containing from 3 to 6 L + doses which had been used on a large scale. By diluting the toxin and thus greatly diminishing the protein content of the mixture, it was hoped to eliminate the objectionable local and constitutional reactions. Zingher stated that, as a result of their investigations, they had come to the following conclusions on the subject, namely, that the new mixture of toxin antitoxin containing 1/10 L + per c.c. gave excellent immunizing results, if it was under-neutralised and prepared so as to correspond in its toxicity to a given standard. This standard of toxicity should be such that 5.0 c.c. will cause acute death of a guinea pig in five or six days, 3.0 c.c. will cause death in six to ten days, and 1.0 c.c. paralysis in fifteen to eighteen days and death in eighteen to twenty-five days. The local and constitutional reactions with the new type mixture (1/10 L +)

were only slight in comparison with those noted with the old type mixtures (3 - 5 L +). The new type could be given to older children and adults without the fear of causing any marked local disturbance. Three doses of 1 c.c. to be given at intervals of seven to ten days, the intramuscular route being preferred to the subcutaneous one, and given as a rule into the arm. Talking of freshly diluted toxin given in three doses of 1/10 M.L.D., he said that it gave poorer results than were obtained even with the less toxic mixtures of toxin-antitoxin.

The results of their investigations also showed that toxoid-antitoxin, the outcome of allowing toxin-antitoxin to stand for a long time in the ice chest and so giving rise to an old, deteriorated toxin, can be of great use in active immunization.

In the Proceedings of the Society for Experimental Biology and Medicine, 1924, Zingher⁽²³⁾ and Park claim to have obtained excellent results as the result of using mixtures containing an old toxin which had given rise to toxoid on standing and had been treated by the addition of 0.1 per cent. formalin according to the suggestion of Glenny and Hopkins, the local injections after the intramuscular injections being only slight and most marked, as one would expect, in positive combined pseudo reactors. Only a

few children showed constitutional symptoms. The local reactions were no more marked than after the use of the new 1/10 L + mixtures, while the immunity results were good and compared favourably with those noted after the use of the 1/10 L + mixtures.

The toxin-antitoxin mixtures used by O'Brien⁽²⁴⁾, Glenny and Allen, etc., in this country, and supplied by Messrs Burroughs and Wellcome, are based on American methods, but are less toxic than the American Official mixtures, as a rule. In 1 c.c. of the mixture there are 3 L + doses of toxin and about 3.5 units of antitoxin, a sample of their current batch showing that three guinea pigs injected with 1 c.cm. were alive and well 30 days later, while of 17 guinea pigs injected with 5 c.cm. of the mixture, 14 showed diphtheritic paralysis, most of them between the twentieth and twenty-ninth day. The injection of this toxin-antitoxin into normal rabbits produced a satisfactory degree of immunity within eight to twelve weeks.

In a communication from O'Brien in November of last year, our attention was drawn to a new preparation of Toxoid Antitoxin which they had in hand and which they considered much more efficient than any other toxin-antitoxin mixture. O'Brien considered that the reactions in adults were less with this

mixture than with ordinary mixtures and the immunizing power higher.

EXPERIENCE WITH TOXIN ANTITOXIN MIXTURES (Adults).

Since September 1922 we have been actively engaged in the immunization with toxin antitoxin mixtures of the staff of the City Hospital, Edinburgh. In Table 9 it was noted that out of a total of 225 nurses schicked, 148 or 65.7% of these were Schick positive reactors. The logical sequence of this naturally is their immunization against diphtheria with mixtures of toxin-antitoxin. The toxin-antitoxin used was the same as that used by O'Brien and his co-workers in most of their work and was supplied to us by Messrs Burroughs and Wellcome.

Of the 148 positively reacting nurses, 132 or 89 per cent. have been immunized with toxin-antitoxin and it is worthy of note that not a single nurse refused to be injected with the full number of doses required. Those not immunized were not available either because they had left the hospital or for some other satisfactory reason.

Small doses of toxin-antitoxin were given to begin with. One small group of three nurses received



doses as follows, .1 c.c., .5 c.c., 1.2 c.c., 1.2 c.c., making 3 c.c. in all. A second small group of three nurses received doses of toxin-antitoxin as follows, .2 c.c., .5 c.c., 1 c.c. and 1.3 c.c.; while a third group of seventeen nurses received three doses as follows, .5 c.c., 1.2 c.c. and 1.3 c.c. each.

The smaller doses on the whole gave much less local and general upset than the larger doses, but the fact that, in some cases only three injections were given, whereas in others four were given, caused a certain amount of disquiet among the staff - the fact that they might have to get four injections, and, as they said, four sore arms, tended to cause a breakdown in the programme. This was largely due to the fact that one nurse in particular, receiving only .2 c.c. of toxin-antitoxin as a first immunizing dose, reacted so severely that the whole scheme of immunization almost fell through. This particular nurse gave, when Schick tested, a very marked pseudo reaction, and, within 24 hours after receiving .2 c.c. of toxin-antitoxin, she complained of violent headache, marked shivering and a feeling of sickness and giddiness, with a temp. of 101. The local reaction consisted of an area of redness of a considerable extent, indurated, tender to the touch and hot and sore, with a feeling of tightness from the very marked swelling.

The injection was given subcutaneously into the upper arm in the region of the insertion of the deltoid, and the redness and swelling extended from above the middle of the upper arm to well below the elbow.

The nurse in question was confined to bed for about 72 hours, and, during that time, she felt very miserable, the headache being severe. During the second 24 hours she vomited repeatedly. The headache was only slight at 72 hours after the injection, whereas the arm still showed moderate redness and swelling but was rapidly improving; 24 hours after this, the nurse was completely recovered and quite well. This nurse received a further dose of .5 c.c. of toxin-antitoxin a week later and reacted even more severely. The course of the reaction was worse locally and the temperature reached 104 about 24 hours after receiving the injection. The headache was very violent, but 24 hours later, or 48 hours after receiving her injection, she was feeling very much better, and by the next day she had practically recovered both locally and generally. This local and general reaction was the worst which I have noticed in almost 3000 injections of toxin-antitoxin given, all of whom received, with the exception of the nurses mentioned above, 1 c.c. as a dose on every occasion. Two nurses who received doses of .1 c.c. to begin with were off duty

when a larger dose was given later: one of these received .1 c.c. and had as a consequence only slight local reaction and no general upset, but when given a second dose of .5 c.c. she had moderate local reaction and a moderate general upset, with temperature about 100⁰ F. She was only off duty half a day. A second nurse was also off duty half a day - in the afternoon - after receiving 1.2 c.c. of toxin-antitoxin as a third dose, the first and second having been .1 and .5 c.c. respectively. She had a local and general upset similar to the first.

The third group of nurses - numbering 17 - gave in several instances moderate local reactions, i.e. an area of redness and swelling extending about six inches or so up and down the arm, and about four or five inches round the arm, but in only one or two was there more than slight headache. These few had moderate headache and slight temperature of about 100⁰ F., but were not off duty.

The remaining nurses, 109 in all, received 1 c.c. doses of toxin-antitoxin at a time - each receiving in all 3 c.c.- at intervals of from five to seven days. There was no reaction which could be classed as very severe, though a good many had considerable reactions both locally and constitutionally. Altogether 20 nurses, or 15.1 per cent., were reported to me as

quite unfit for duty in the wards. They were kept in bed in the Nurses' Home for an average of two days after either the first or second injection. Only three nurses were off duty after both the first and second injections: only one nurse - mentioned before - was warded, being in bed for three days after each injection of toxin-antitoxin. Twenty-three others, though feeling pretty seedy, continued on duty.

I have classified the local and general reactions as follows:-

TABLE 10.

Maximum Local Reactions (from all injections).

No. of
Nurses.

A	2	<u>Nothing</u> to see.	
B	43	<u>Slight</u> local redness, induration and feeling of heat in the part; very little swelling, only a little sore; redness, etc. lasting just a day or two.	} Later - slight itchiness, desquamation and discolour- ation.
C	73	Moderate local redness, induration and swelling; somewhat hot to the feel and sore; area of redness and swelling about 6 or 7 inches in diameter; redness, etc. lasting about 2 days or so.	} Later - itchy as a rule, with desquamation and discolour- ation.

TABLE 10, Contd.

		No. of Nurses.	
Fwd.	118		} Later - itchy, desquamation and discolouration.
D	14	Fairly severe local reaction; redness, swelling, etc., extending from half way up the upper arm almost to the wrist; very sore and uncomfortable; very hot to the feel; condition lasting 3 to 4 days.	
E	0	Very severe, worse than any reaction described above, so severe as to be a surgical condition.	}
Total	132		

TABLE 11.

Maximum Constitutional Disturbance (from all injections).

		No. of Nurses.	
I.	44	Nothing at all.	
II.	45	Slight headache and feeling of malaise; probably no temperature or only 99° F., malaise lasting only 48 hours at the outside.	
III.	33	Moderate upset, with headache and some shivering, aching limbs, slight giddiness; temperature of about 100° or so; upset lasting about 48 hours, and beginning within 24 hours.	
IV.	9	Fairly severe headache and shivering; aches in limbs; sickness and vomiting; Temperature 102° or so; upset comes on within 24 hours and lasts about 48 hours, when quite well.	
V.	1	Very severe with violent headache, rigor, aches all over, vomiting; temperature 104°; absolutely prostrated; upset comes on within 24 hours and lasts 48 to 72 hours; quite well afterwards.	
Total	132		

These two Tables 10 and 11 explain themselves and show the actual number of nurses who suffered from a local or constitutional reaction out of the 132 injected.

TABLE 12.

Maximum Local and General Reactions (Grouped).

	A	B	C	D	E	Totals	Nurses off duty (Incapacitated)
I.	2	29	13	0	0	44	None
II.	0	13	31	1	0	45	None
III.	0	1	24	8	0	33	12 off duty; average 2 days.
IV.	0	0	5	4	0	9	7 off duty; average 2 days. (other 2 sick at home)
V.	0	0	0	1	0	1	1 off duty twice for 3 days.
Totals	2	43	73	14	0	132	20 off duty (and 2 sick at home).

Nurses ages 17-27.

Table 12 is a combination of Tables 10 and 11 put together and shows the number of nurses who had local reactions and whether or not they suffered from constitutional disturbance at the same time. It will be seen from a study of this Table that two

nurses who had no local reaction had also no constitutional disturbance; that of 43 nurses who had slight local reaction, 29 were quite well and 13 had slight general upset, while only one had a moderate constitutional reaction; that of 73 nurses who had moderate local reaction, 13 were quite well, 31 had slight constitutional reaction, 24 had moderate upset and 5 had a fairly severe general reaction; and that the 14 nurses who had a fairly severe local reaction had also a general reaction, and of these 1 had only a slight constitutional upset, 8 had moderate general upset, 4 had a fairly severe constitutional upset and only 1 a severe constitutional reaction, necessitating being warded for three days twice.

The Table also shows the relationship between those off duty - incapacitated - and the constitutional upset.

TABLE 13.

Nurses.

Incapacitated rate from Toxin-antitoxin, in relation to previous Diphtheria and Pseudo Reactions.

	Number	Previous Diphtheria Percentage	Pseudo Percentage	Incapacitated Percentage
Total Nurses	132	19.2	40.1	15.1
First Group	86	25.5	46.5	22.0
Second Group	46	13.0	28.2	2.1

Table 13 is interesting. It shows that the total number of nurses who received toxin-antitoxin - 132 in number - has a previous diphtheria rate of 19.2 per cent. and a pseudo rate of 40.1 per cent., and that the percentage incapacitated and rendered unfit for duty is 15.1. I have divided the total number of nurses into two groups of 86 and 46 nurses respectively, called First Group and Second Group. The first group of nurses represents nurses who had been in hospital a considerable time (some, two to three years previous to being Schick tested and immunized). Many had taken diphtheria while in hospital and so had a fairly high pseudo rate as the result of being sensitized to protein. This group of nurses had an incapacitated percentage of 22.0. In comparison with this is the second group of nurses, who were Schick tested as soon after arrival in hospital as possible. They show in Table 13 a much lower "Previous Diphtheria" and "Pseudo Percentage" rate, and it is interesting to note that the "Incapacitated" rate is very much smaller, and in fact is almost negligible. It has become a rare thing now, in the process of immunizing the new Schick positive nurses on their arrival in hospital, to have one off duty as a result of the injections. This shows the effect which previous diphtheria and antitoxin has in sensitizing the individual.

TOXIN - ANTITOXIN MIXTURES IN CHILDREN.

In conjunction with the above immunizing work among the nurses at the City Hospital, I also immunized a group of 312 children in that institution. The age groups of these children were as follows:-

	<u>Number</u>	
0-5 years	183	} 287 under 10
5-10 years	104	
<u>10-15 years</u>	<u>25</u>	
Total 0-15 years	<u><u>312</u></u>	

These children, all positive Schick reactors, gave a pseudo reaction of only 1.6 per cent., but as many of the children had been read on the fourth day, this figure is inaccurate. As mentioned previously, the pseudo rate for this age group 0-15 would be estimated at not more than 3.5 per cent. - see Pseudo Reaction Table 8. This is a low rate as compared with the nurses pseudo reaction rate of 40.1 for those immunized - age group 17-27.

On the 312 children, only 17 had small initial doses of toxin-antitoxin. The reactions were so negligible in these that the remaining children were given doses of 1 c.c. at a time, at intervals of five

days, till 3 c.c. of toxin-antitoxin had been injected.

Practically all the children received their full amount of toxin-antitoxin; only a few left hospital before the completion of the immunization.

TABLE 14.

Grouped Maximum Local and Constitutional Reactions
of 312 Children: Age Group 0-15.

	A	B	C	D	E	Totals	
I.	99	147	6	0	0	252	(80.7 per cent)
II.	11	40	4	0	0	55	(17.6 per cent)
III.	0	5	0	0	0	5	(1.6 per cent)
IV.	0	0	0	0	0	0	-
V.	0	0	0	0	0	0	-
Totals	110	192	10	0	0	312	Grand Total

Table 14 shows the maximum local and constitutional reactions of 312 children immunized with toxin-antitoxin. The letters A, B, C, D, E, and I., II., III., IV., V., indicate much the same degree of severity of the local and general reactions respectively as in the case of the nurses, the only

modification being that, as far as the general upset is concerned, II. means slight rise of temperature to the neighbourhood of 99° , with perhaps slight fretfulness, and III. means rise of temperature to the neighbourhood of 101 or 102° , without very much else to show.

Table 14, then, shows that, out of 312 children, 110 suffered no local reaction at all, and of these, 99 showed no general upset of any kind. The temperature remained normal and the children were not even fretful: there was no disturbance of appetite or sleep, in fact the children were apparently quite normal. The remaining 11 children showed only a very slight upset of temperature from the subnormal to the normal line, but otherwise they were apparently quite unaffected by the injections.

We also see from the Table that 192 children out of the 312 injected suffered from slight local reaction, and of these, 147 showed nothing at all at any time as regards upset of temperature, sleep, appetite, etc., while 40 showed only a very slight upset of temperature and one or two were fretful; and the remaining 5 showed a moderate general upset, i.e. rise of temperature to the neighbourhood of 102° F. In only two of these could one be certain that the rise of temperature and fretfulness of the child were

caused by the injection of toxin-antitoxin. In each case the temperature subsided in a few hours and the child was quite well; there was no sickness.

The 192 children mentioned as having slight local reactions had very little to see on the arm, and the maximum reaction was an area of redness about three inches in diameter, a little hot to the feel, but this soon disappeared and left in a few cases a little bluish discolouration and desquamation.

And again, we see from the Table that 10 children are noted as suffering from a moderate local reaction of about six inches in extent, somewhat red and swollen looking, but fading in a day or two, leaving some staining and desquamation at the site of the injection. Of these 10 children, 6 suffered no general upset at all, not even a flicker of temperature, while 4 showed only a rise of temperature to the neighbourhood of 99° , but were quite well. Not a single child had even a fairly severe local or general upset.

In the course of immunizing these children it soon became evident that the local reaction was not a thing to worry much about, and that the number of children - at least up to ten years of age - who were made ill by the injections was infinitesimal. To put it briefly, 96.7 per cent. of the children either had none or only a slight local reaction, while no

child who was injected even had more than a moderate local reaction at the site of injection, a reaction which lasted only two or three days and which gave very little trouble. The injections were all given subcutaneously into the outer side of the upper arm, but if the toxin-antitoxin was given so superficially as almost to be intracutaneous, there often remained some pigmentation, just as in the case of the Schick test. The most severe local reactions left as a rule some bluish red staining and desquamation at the site of the injection.

As far as the general upset of these children was concerned, how slight that was may be gathered from the fact that 80.7 per cent. of them had not even the slightest upset of temperature, that 17.6 per cent. had only the smallest rise of temperature possible, i.e. from subnormal to normal or even to 99° , while only 1.6 per cent. had rises of temperature to the neighbourhood of 101 or 102° F., with very little to show for it.

TABLE 15A.

Percentage of Local Reactions (diagramatic)

in First Group of Nurses (Red):

Pseudo rate 46.5 per cent.

Second Group of Nurses (Black):

Pseudo rate 28.2 per cent.

Group of Children (Green):

Pseudo rate 3.5 per cent (for age group).

First Group of Nurses = 86 in number)
 Second " " = 46 " ")
 Group of Children = 312 " ")

ages 17-27.

ages 0-15.

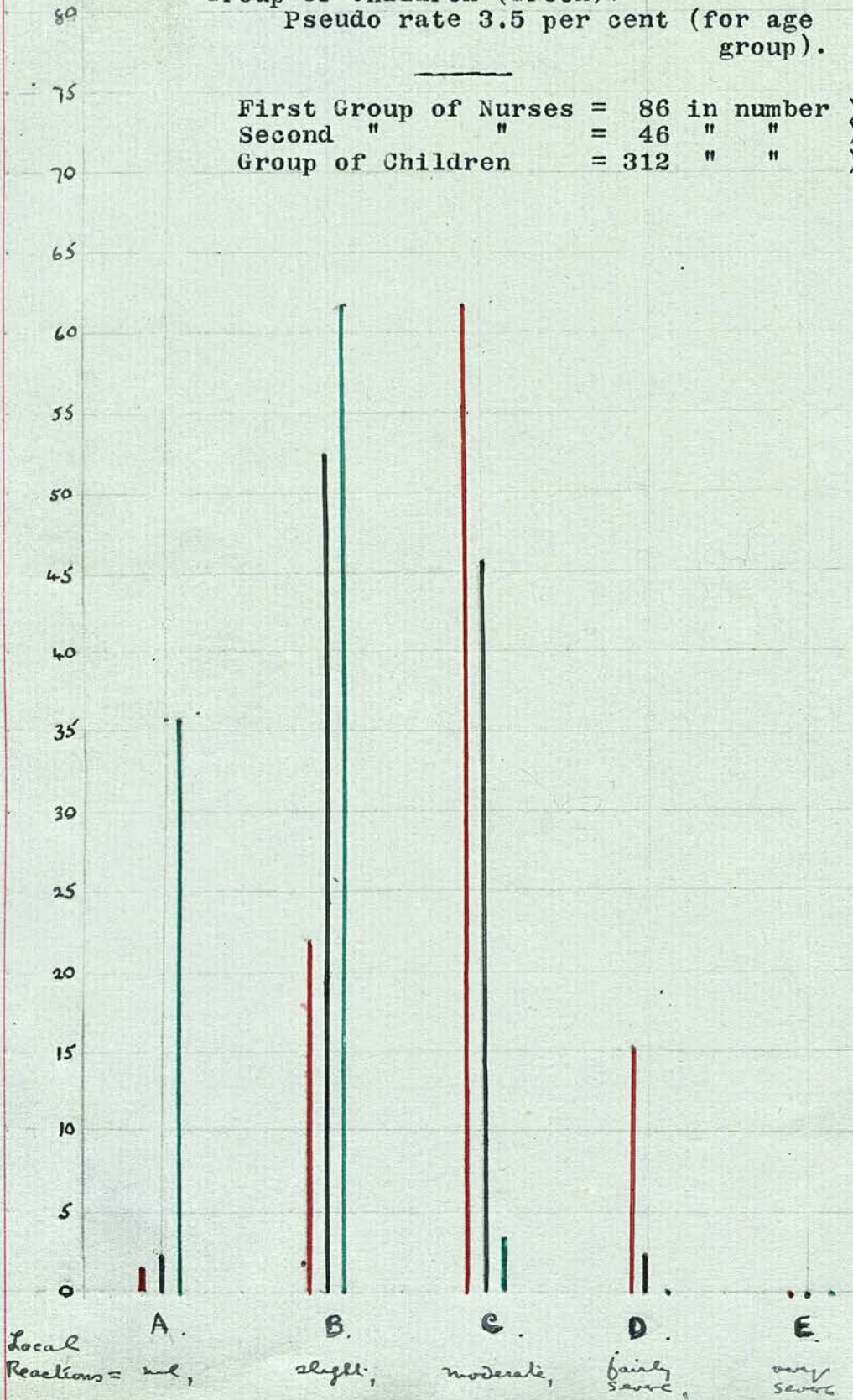
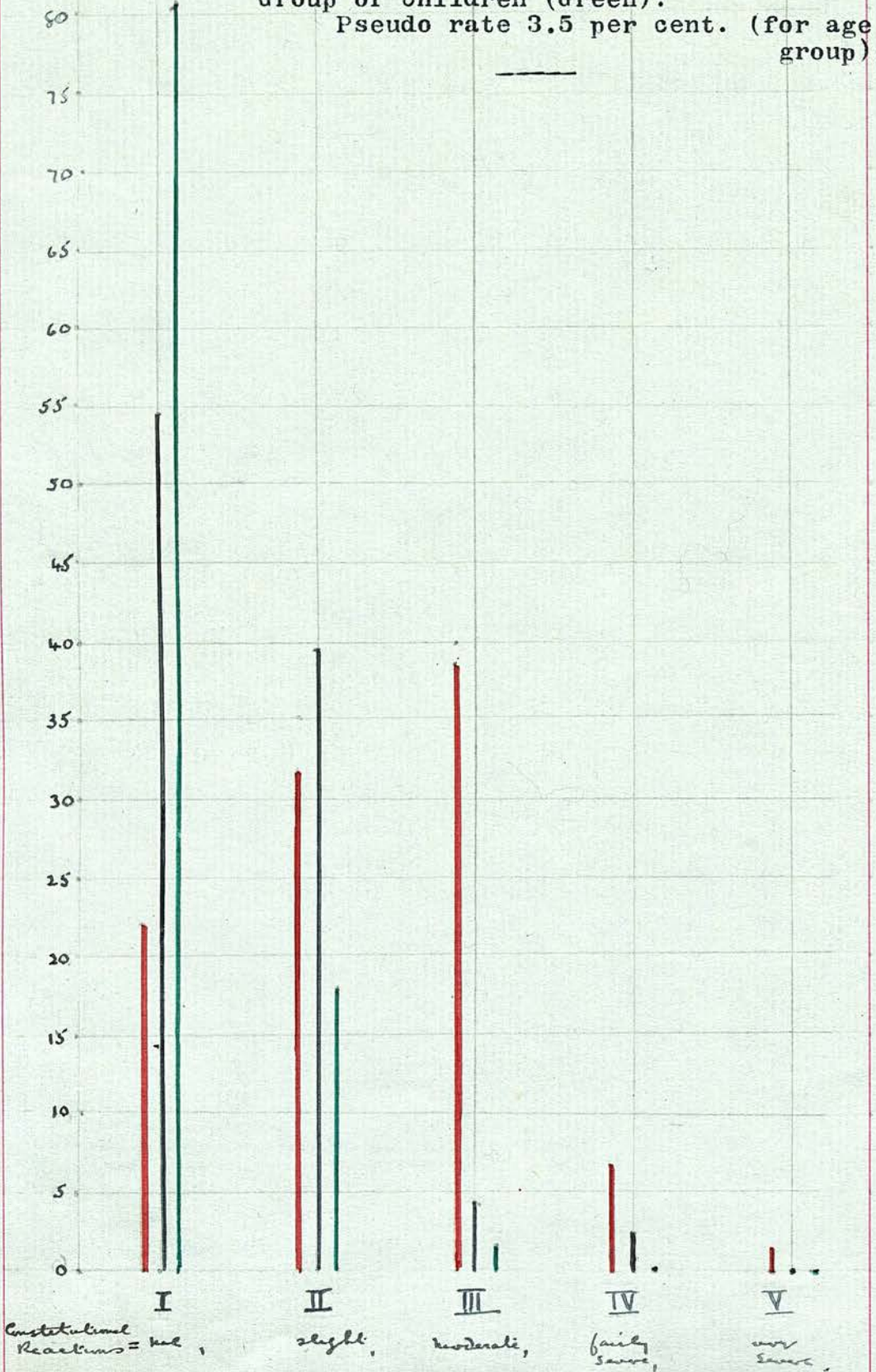


TABLE 15B.

Percentage of Constitutional Disturbances (Diagrammatic)

in First Group of Nurses (Red):
 Pseudo rate 46.5 per cent.
 Second Group of Nurses (Black):
 Pseudo rate 28.2 per cent.
 Group of Children (Green):
 Pseudo rate 3.5 per cent. (for age group).



The diagrams 15A and 15B show the differences in reaction as regards local and constitutional disturbance between groups of adults and children. The first group of nurses - marked red - react more severely than the second group - marked black -, while the children - marked green - hardly react at all and contrast markedly with the nurses as a whole. The first group of nurses represent, as stated already, those who had been in hospital a long time before being Schick tested and immunized, and the second group represent nurses who were Schick tested and immunized as soon after arrival in hospital as possible. Their pseudo rates are seen on Table 13, and the reactions to toxin-antitoxin in 15A and 15B., in contrast to the reactions of the children.

DIFFERENCES IN REACTIONS BETWEEN FIRST, SECOND
AND THIRD DOSES OF TOXIN - ANTITOXIN
IN A GROUP OF ADULTS.

The children reacted so little that no difference could be made out between any of their doses, but the nurses showed differences in reaction with each dose.

A group of 109 nurses, all receiving three doses

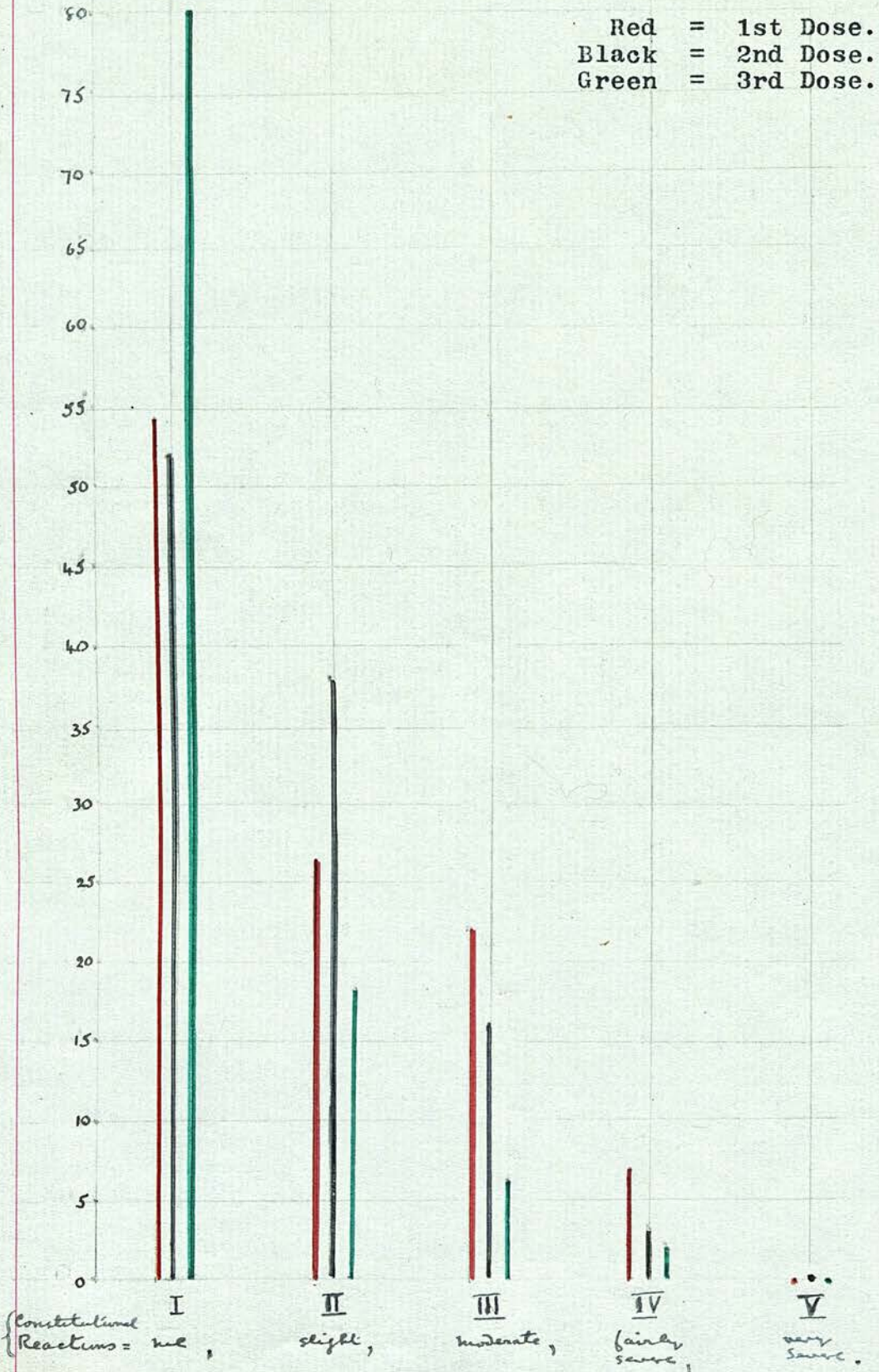
of 1 c.c. each, were observed to see which dose gave the most reaction, and caused the greatest upset, and it was found that the second dose of toxin-antitoxin as a rule gave a more severe local reaction than the first, but that the third gave the least trouble of all. The doses were given at intervals of from five to seven days into alternate arms, in doses of 1 c.c. at a time.

As regards the general upset from the different doses, while the general tendency was for the second dose to give less trouble than the first in contra distinction to the local reaction, yet it was never safe to say that the feeling of malaise and headache might not be as bad at least. The third dose of toxin-antitoxin, on the other hand, practically always gave much less trouble in this respect than either of the other two, and this is well shown in the subsequent Table (16) where it can be seen that, whereas about 50 per cent. of the nurses had no constitutional upset with either the first or the second dose, the percentage of those who were unaffected by the third dose went up to about 80, and very few nurses had fairly severe reactions - less than 2 per cent in this group of 109. - while a great many of those who showed a slight or even moderate reaction with the second dose, usually had no upset at all with the

third. Some, of course, reacted to a moderate degree with every dose.

TABLE 16.

To show the Numbers of Nurses who had Constitutional Disturbance (if any) after each Dose of Toxin-Antitoxin out of a Group of 109 Immunized with 3 c.c. (1 c.c. at a time).



The pseudo rate of this group of 109 nurses immunized, and whose reactions are shown diagrammatically in Table 16, was 40 per cent., so that we have here a very fair index of the maximum reactions to be expected in immunizing an adult population of this type. The nurses could usually be assured, when getting the third dose of toxin-antitoxin, that they would suffer very little discomfort, while those nurses who gave no pseudo reactions came to know that they would not be troubled very much, with any of the injections, either locally or otherwise. Occasionally, of course, a nurse without a pseudo showed some reaction, but even when the arms were troublesome they, as a rule, were little upset otherwise. They, in fact, were very like the children in their response to the toxin-antitoxin. It would obviously be a great advance if the protein constituent of toxin-antitoxin could be got rid of.

Hoping to find a mixture which would give little trouble, I asked Dr O'Brien to send us a small amount of toxoid-antitoxin. I took the opportunity of trying the effect of it on a group of adults (including one of the medical staff) and 11 children. The children, as in the case of the toxin-antitoxin, showed very little upset of any kind, while the adults seemed to give much similar reactions, both locally

and as regards headache, etc., as those who had received toxin-antitoxin. The reactions might be described as moderate reactions; none could be described as severe. I will refer to its immunizing properties later.

As a result of the immunization of this fairly large group of 312 children in the Hospital, we were able to advise the Public Health authorities of Edinburgh that they could safely give such mixtures of toxin or toxoid-antitoxin to school children from 5-10 years of age, and this has been borne out in subsequent work among the school children both in Leith and Edinburgh, of whom several thousands have been Schick tested and a very large number immunized.

MEDICAL STAFF.

In the course of this work there have been many changes in the Medical Staff and most of the resident medical officers have been tested, and immunized if they required it. As a result we have a group of 25 adults, of whom 19 (or 76 per cent) were Schick positive and with a pseudo rate of 52 per cent. Seventeen of these have been immunized. The reactions have varied with the size of the pseudo reaction

and, while some have been slight, others have been fairly severe. One member of the staff reacted curiously. He had a very marked pseudo reaction and naturally it was with some trepidation that 1 c.c. of toxin-antitoxin was given as a first dose, but, though there was some slight redness after the first injection, followed by troublesome itching, yet there was no constitutional reaction at all after any of the injections. When reschicked later, on two occasions he was a negative Schick reactor without a pseudo. Why there should be no pseudo reaction on reschicking after being immunized was difficult to understand, as I have noticed quite a number of our nurses, who had no pseudo reaction before being immunized, later showed a susceptibility to protein-derived presumably from the toxin-antitoxin mixtures and the toxin of the Schick test. A good many, on the other hand, have never shown a pseudo reaction at all either before or after immunization.

As mentioned previously, different kinds of mixtures have been tried, especially by Schroeder⁽²⁵⁾ and Park in New York, with the object of finding out the least toxic mixture which would yet give good immunising results.

O'Brien informs me, in a communication received from him recently, that he is constantly experimenting

to try and find better mixtures for immunization purposes. In the endeavour to make a mixture which will, after one injection, produce rapid and satisfactory immunity, it may of course be found that the more efficient mixtures are more apt to cause reactions. The ideal mixture would be one with low protein content which would give good immunizing results with one or even two injections, especially as regards the immunization of nurses and others employed in fever hospitals, and in the case of older children of the 15-20 age group. The toxin antitoxin mixtures at present supplied by Dr O'Brien from the laboratories of Messrs Burroughs & Wellcome are quite satisfactory for school children of age group 5-10, and also of course for children under 5. We can say this quite confidently as a result of our experience with these mixtures.

Schroeder and Park in their paper on the comparative merits of old and new preparations of toxin-antitoxin, point out the advantages of the new preparations which they were using, containing $1/10$ L + dose of toxin, and show the local reactions and general upset caused by this mixture of toxin-antitoxin as compared with the older preparations. They point out at the same time the better immunizing results with this new mixture. They showed that, as regards

children, the older preparations containing 3 to 5 L + doses gave a much larger percentage of reactions than the new mixtures containing 1/10 L + dose.

TABLE 17.

Children.

Percentage of Local Reactions with 1/10 L + amount of Toxin in the Mixtures as compared with the Percentage of Local Reactions found in City Hospital, Edinburgh.

	Reaction	Schroeder and Park New Mixture. Percentage	Mixture used in City Hosp. Edinburgh. Percentage
	Nil	25	35.2
	Slight	64	61.5
	Moderate	11	3.2
(fairly severe)	Marked	0	0
(very severe)	Very marked	0	0

Table 17 shows the percentages in two groups of children of the local reactions from toxin-antitoxin mixtures. Schroeder and Park were using their new mixture containing 1/10 L + dose, while we were using the mixtures supplied by Dr O'Brien (3 L + doses). It will be seen that the reactions were even fewer among the children in the City Hospital than Schroeder showed with the new preparations, and that both groups

of children reacted very slightly indeed. There were no severe reactions in either group.

Schroeder and Park also found that the new mixtures were very much better for adults than the old ones, for, whereas with the old preparations, among a group of adults, 36 per cent. show marked (or fairly severe) reactions and 13 per cent. showed very marked (or very severe) reactions, with the newer preparations these figures were 10 per cent and 1 per cent. respectively.

TABLE 18.

Adults.

Percentage of Local Reactions with 1/10 L + Dose of Toxin in Immunizing Mixtures as compared with Local Reactions from Mixtures used in City Hospital, Edinburgh.

Reaction	Schroeder and Park Mixture. Percentage	Mixture used in City Hosp. Edinburgh. Percentage
Nil	0	1.5
Slight	44	32.5
Moderate	20	55.3
(fairly severe) Marked	10	10.6
(very severe) Very Marked	0	0

The Table 18 shows the local reactions in two groups of adults. Schroeder and Park were using their new mixture which gave many fewer "marked" reactions and no "very marked" ones as compared with their older preparations, and we were using the same mixtures as in the case of the children.

It will be seen from a study of Table 18 that more nurses reacted moderately in our figures than in Schroeder and Park's and that correspondingly they showed more **adults** who had only slight reactions than we have done.

DANGERS OF TOXIN - ANTITOXIN MIXTURES.

It can be confidently stated, after a personal experience of almost 3000 immunizations in the City Hospital, Edinburgh, and among the school children of Edinburgh and Leith, that I have not seen a single individual ultimately any the worse for having been injected with toxin-antitoxin. Even the nurse who reacted most severely was quite fit and on duty almost the moment her temperature was normal. Only in one nurse was there a slight superficial abscess formed at the site of injection, and this was probably quite accidental, as nothing beyond slight bruising,

some pigmentation and slight desquamation occurred after any other injection, after the acute local reaction, if it occurred, had subsided.

No fatalities have been reported as having occurred in this country as the result of the use of toxin-antitoxin mixtures, but in one district in America eight or ten children are reported to have died as the result of immunizing doses, while others showed sloughing arms and transient paralysis. In a communication which we received from Zingher concerning this accident, he informed us that there had been a mix up either in labelling the specimens or in tagging the animals on which the mixtures were tested before the toxin-antitoxin mixtures were sent out by the firm making the stuff. On examination of the mixtures afterwards, it was found that there were 20 M.L.D. of toxin in each dose, enough to kill a young child.

Errors of this kind have been eliminated in the United States by means of proper supervision. Specimens of each lot of toxin-antitoxin prepared by different laboratories must now be sent to Washington to be "tested out" before the preparations can be distributed.

In the same communication Zingher told us, on enquiry, about another accident which resulted in

about 40 children suffering from sloughing arms and a few developing transient paralysis. This accident was due to, apparently, the fact that certain phials of the mixture, after having passed all the usual tests, were exposed during very cold weather to temperatures of 0° F. or lower. Hundreds of other phials, not exposed to low temperatures, were used in other cases and produced no unusual reactions. Laboratory experiments showed that, while a short period of freezing did not materially affect the toxin-antitoxin mixture, severe freezing for 18 hours apparently caused the antitoxin to dissociate from its combination with the toxin. It was found on further investigation that it was the special toxin which was the cause of the particular behaviour of the toxin-antitoxin on freezing.

The toxin-antitoxin mixtures used in the City Hospital are always kept in the ice chest at a suitable temperature and have given no trouble.

TESTING AND IMMUNIZATION AMONG SCHOOL CHILDREN.

At the beginning of the year we began Schick testing the children - age group 5-10 - attending the Board schools of Leith and Edinburgh. From time to

time small epidemics of a virulent kind of diphtheria had occurred in one of the schools, and so the ground was prepared for the work, several children having died in the hospital.

The Schools were chosen as a suitable place for the work, as there the children are easily got at. Consent slips were issued for the parents to sign, giving the M.O.H. or his representatives permission to test and immunize the children against diphtheria.

TABLE 19.

A Number of Children in Board Schools Tested and Immunized.

School	No. of Children under 10 at School	Consent percentage by Parents	Number Schick Tested	Per Cent. Positive Schicks	Social Quality of the School	No. receiving 3 c.c. T.A.	No. receiving 2 c.c. T.A.	No. receiving 1.c.c. T.A.	Total No. receiving T.A.
School Y.	480	22.2	108	34.2	Very Poor	30	2	5	37
School C.	-	-	204	47.0	Poor	90	2	3	95
School B.	340	38.2	131	54.1	Poor	68	-	-	68
School B.H.	-	-	209	74.8	Good	119	17	11	147
Totals			652			307	21	19	347

Table 19 shows four Schools in which testing and immunizing was done. It will be seen that, out of 480 children between the ages of 5-10 attending school Y., only 108 were tested by means of the Schick test; and, out of 340 children attending school B., 132 were tested (similar figures for the other two schools are not available). The reason for this of course is that the parents were somewhat unwilling to have their children tested, probably because many of the fathers had had injections while in the army and had frightened their wives with harrowing stories about doctors and hospitals. This state of affairs will improve as the public gain confidence in the procedures.

The percentage of positive Schicks was very striking. The poorest school in the district gave the smallest number of positives, and the one which was attended by good class children gave a high percentage of positive Schick reactions. The percentage of positives among girls attending this last school was as high as 83.3, while the percentage of positives among boys was 68.9 out of a total of 209 children tested. Zingher has pointed out this fact about the effect of social surroundings on the susceptibility to diphtheria. It has also been well shown in previous tables.

The testing and immunizing was carried out without much trouble. The teachers loyally co-operated in the making of lists and in assisting generally, i.e. wiping the arm with a pledget of cotton wool soaked in ether, calming frightened children and arresting the tears - which there were occasionally. The children were very good indeed. No injection was ever followed by the slightest sign of sepsis.

The reactions, as far as could be judged, were much the same as in the group of children done in the City Hospital. At first teachers and parents were inclined to make the most of trivial reactions, but, after the novelty of the affair passed off, we had no trouble at all.

The Table - 19 - shows that out of 347 children who received their first dose of toxin-antitoxin, no fewer than 340, or 88.4 per cent., completed their immunization. This shows that the reactions were not sufficiently troublesome to prevent the vast majority from receiving all three doses of toxin-antitoxin. The children usually received the first dose a week after being Schick tested. At first we read the reaction on the fourth and tenth days after testing, and gave the first dose of toxin-antitoxin on the tenth day, and 1 c.c. afterwards at intervals of a week, but latterly we found it quite a good plan to

give the first dose of toxin-antitoxin to the positive reactors at the time of doing the reading - a week after being tested - and at intervals of a week afterwards. The severity of the local reactions could always be judged if, when giving the subsequent injections, there was anything remaining in the arm, which had received the dose a week previously, in the shape of bluish discolouration and desquamation, the extent of both of these being a good index of the nature of the reaction. Only in a few cases was there any sign of the reaction being more than moderate at the worst. No serious complaint was sent to us about any child.

The number of children absent from school as a result might also be a fair index of the severity of the reaction, but I doubt if this is much guide as far as children are concerned, as some children might be kept at home for no very obvious reason other than that the arm looked sore, the child instead of being at school usually spending its time playing in the street. Roughly speaking, in one school about 18 per cent. of the children were absent on the day following the first dose of toxin-antitoxin, 35 per cent. after the second dose, and none after the third dose; while in another school, 22 per cent. were absent the day following the first dose, 38 per cent. after the second, and 7 per cent. after the third dose of toxin-

antitoxin. In both schools, then, more children were off school with the second than with the first injection, while only a few were off on account of the third. None of these children off school had anything beyond what was termed a "sore arm".

Many other schools were visited for the purpose of testing and immunization purposes. The schools mentioned above were under my own supervision.

Far from our visits being dreaded, the children used to look forward to them, as, during the hour when the readings or injections were being made, they had no lessons.

It is too early yet to speak of the results to be obtained from these inoculations in the schools, which were only completed before the summer holidays.

IMMUNIZATION RESULTS.

The toxin-antitoxin mixtures which have been in general use in this country and in America have taken many weeks and often many months to produce their immunizing effect, but the hope is that new mixtures will soon be found which will not only give little trouble but which will produce immunity in the shortest possible time. The cutting down of the number of the doses is also a thing to strive after.

TABLE 20.

Toxin-Antitoxin Immunization Results, showing Percentage developing Immunity, of two groups of Children in a Children's Home in Edinburgh.

Age Groups of Children in Years	Number of Children tested	Schick Positive percentage	Number of Children receiving T.A.	Percentage of general upset	Percentage developed immunity		who im- in 22-24 weeks
					in 8-10 weeks	in 16-18 weeks	
5-10	75	61.3	41	10	63.4	82.9	92.6
10-15	124	41.9	51	25	58.82	87.7	90.2

This Table shows two groups of children in a Children's Home in Edinburgh. They were Schick tested towards the end of last year and the positive reactors were immunized. It will be noticed that the positive Schick rate was 61.3 per cent. for the age group 5-10, and 41.9 per cent. for the age group 10-15. There was a reaction in the shape of headache, faintness, lack of appetite and slight temperature in 10 per cent. of those immunized between 5 and 10, and in 25 per cent. of those immunized between 10 and 15. There were no very severe reactions. It will be noticed that, on reschicking those children at from 8 to 10 weeks after receiving their immunizing doses of toxin-antitoxin, 63.4 per cent. of those who had originally been Schick positive were negative reactors,

and that this percentage increased to 82.9 per cent. at 16-18 weeks, while at 22-24 weeks, 92.6 per cent. of these children were negative reactors; and further, of those children who were originally Schick positive - of age group 10-15 - and who received doses of toxin-antitoxin, 58.8 per cent. were negative reactors at 8-10 weeks, and this percentage had increased to 87.7 at 16-18 weeks, while at 22-24 weeks, 90.2 per cent. of these children were immune to diphtheria as indicated by the Schick test. Those still positive were immunized with further doses of toxin-antitoxin, and we await the result of their reschicking with interest.

TABLE 21.

Nurses - City Hospital.

Showing (1) Number retested after T.A.
 (2) Time of retesting.
 (3) Percentages of the Immunes at different times.

Number of Nurses Immunized	Number Retested	Time of Retesting after T.A.	Percentage Negative
132	93	3-5 months	68.0
	77	6-9 months	84.4
	38	12-21 months	94.0

Table 21 shows that, of 132 nurses immunized, 93 being still in hospital were retested from 3-5 months after receiving immunizing doses of toxin-antitoxin, and that 68. per cent. were immune; that 77 of the nurses being still in hospital were tested again at 6-9 months after toxin-antitoxin, and that 84.4 per cent. of these were immune; and that 38 being still in hospital were retested at 12-21 months after toxin-antitoxin, and of these 94. per cent. showed a negative Schick reaction. Those not retested were not available for one reason or another.

The 38, who were retested on the last occasion and who gave a percentage of 94 immunes, were all noted as negative reactors at the previous time of being tested - months before. Two of these at this retest gave an undoubted positive reaction, one of them being noted previously as a negative reactor without a pseudo, and the other a negative reactor with a pseudo. The first one may be taken to have relapsed - assuming that there was no fault in technique on the former occasion; the second nurse is probably a border line reactor and a small difference in size of dose of test and control solution might make a reaction negative one time and positive the next in certain cases. Six other nurses in this group of 38 gave doubtful reactions, but were ultimately called

negative and pseudo at this last time of testing. They had previously been called negative and pseudo when tested months before.

Zingher⁽²⁶⁾ states that small differences between test and control may have no significance, and that variations in the protein content of the test and control solutions, or variations in the technique, where different individuals make the Schick test and the control test, may account for these slight differences on the two sides. Marked differences, he says, however, in which the area of redness at the site of the Schick test is always more pronounced and has the other characteristic appearance of a positive reaction, should lead one to interpret the Schick reaction as positive combined. I have previously indicated how difficult these combined reactions are to read. They raise so much doubt in one's mind as to the reading that we have decided in future to dispense with the reschicking of the nurses in the City Hospital for a considerable time after being immunised, and instead to give a further dose of toxin-antitoxin to all nurses three months after their third dose and to count them as immune for all practical purposes. A retest could be done six months after this, and any remaining positive receive one more dose of toxin-antitoxin.

P. H. Kramer⁽²⁷⁾ records the results of Schick testing and immunization of the nursing staff at the Rotterdam Municipal Hospital and, in consequence of two sisters having taken diphtheria who were noted as being negative reactors, he has decided not to perform Schick reactions any more, but rather to treat all persons likely to be exposed to diphtheria infection with toxin-antitoxin without Schick testing, as at the Wilhelmina Hospital, Amsterdam. I would not advocate going as far as this. I consider that it is worth while testing the nurses on arrival in hospital with the Schick test, as they - being probably fresh from the country - show a considerable number of clear cut negative and positive reactions. I consider that anything doubtful should be called positive at this first test, and I am of opinion that four doses of toxin-antitoxin at least should be given to Schick positive nurses in fever hospitals, the last dose to be given three months after the third dose: retesting to be done six months later if necessary, and those still positive to get a further dose of toxin-antitoxin.

TABLE 22.

Toxin-Antitoxin Immunization Results.
 Small Group of Children in a Children's Home in
 Edinburgh which developed immunity very slowly.

Age Groups of Children in Years	Number of Children Tested	Schick Positive Per- centage	Number receiving. T.A.	Percentage developing Immunity	
				in 2 mths.	in 6 mths.
5-10	21	66.	14	35.7	42.8
10-15	17	64.7	11	40.	50.

This small group of children was notable for the fact that they gave, on being Schick tested, extraordinary well pigmented reactions, indicating therefore that they were highly susceptible.

It will be seen that, while at two months after immunizing doses were given 35.7 per cent. of those in age group 5-10 were immune, yet, at six months, this percentage had only increased to 42.8; and in the case of the 10-15 age group, an immune percentage of 40 at two months after toxin-antitoxin had only advanced to 50 per cent. at six months. This is probably due to the fact that these children were specially susceptible to diphtheria and had not been in contact with infectious disease very much, and so their tissues had not formed the habit of reacting and producing antibodies. Further doses of toxin-

antitoxin have been given to those still Schick positive.

IMMUNIZATION RESULTS WITH TOXOID - ANTITOXIN.

In a small group of 8 adults who received toxoid-antitoxin, the number of those who were negative reactors at 4-6 weeks afterwards was 42.8 per cent. Unfortunately those still positive or doubtful had either left hospital or were unavailable for further testing.

A small group of 11 children - all under 10 years of age - who were immunized with toxoid-antitoxin were reschicked at weekly intervals afterwards.

TABLE 23.

Children.

Toxoid-Antitoxin Immunization Results.

Total Children	Positive	Negative	Per cent. Negative	Time After Toxoid Antitoxin
11	6	5	45.4	3 weeks
11	5	6	54.5	4 weeks
11	4	7	63.6	5 weeks

Table 23 shows this small group of 11 children, with the numbers and percentages immune at 3, 4 and 5 weeks after toxoid antitoxin. It will be seen that 63.6 per cent. were negative at 5 weeks. These children were all clear cut positives on being schicked at first and never afterwards developed any pseudo reaction - unlike so many of the nurses.

RATE AND DEGREE OF IMMUNIZATION.

In this work we have used only the Schick test as a means of estimating whether or not there was any antitoxin in the blood of the individual. The antitoxin content of the blood can be estimated by means of Zingher's⁽²⁸⁾ modification of Roemer's method, and by it as little as 1/200 unit of antitoxin can be determined. It is an intradermic test in guinea pigs, and is economical. Doubtful Schick positive reactors might have the antitoxin content of their blood tested in this way, while the rate of the production of antitoxin could also be found out. This rate varies under different circumstances. It is admitted, for instance, that when the blood contains passively transmitted antitoxin, the action of toxin-antitoxin is interfered with, probably because the mixture after

injection is over neutralised too much to allow it to stimulate the production of antitoxin (Zingher⁽²⁹⁾). Probably it is for this reason that infants under six months of age are considered unsuitable subjects for immunization with toxin-antitoxin mixtures. In this connection it is interesting to note the following case.

A nurse, S., was noted as Schick positive without a pseudo on 19/2/23. She received 1 c.c. of toxin-antitoxin on 7/4/23. On 9/4/23 she showed patching on both tonsils and stated that she had begun to feel her throat sore first on 6/4/23, but she had not reported sick. She received 4000 units of antitoxin on the 9/4/23, when she was warded, and this dose was repeated next day. The throat cleared up in due course and she progressed satisfactorily. I gave her a second dose of 1 c.c. of toxin-antitoxin on 16/4/23, and a third dose on 21/4/23. She was reschicked on 18/7/23 when she showed still a definite positive Schick without a pseudo reaction. Being detailed for duty for a year at another hospital, she missed being reschicked till 5/8/24, when she showed the same reaction to the Schick test as before, i.e. a definite positive without a pseudo. She has been immunized with further doses of toxin-antitoxin.

In this case, then, apparently there has been no

production of antitoxin arising either from the attack of diphtheria or from the injection of toxin-antitoxin, probably because the mixtures when injected were neutralised by the antitoxin.

It is customary in the City Hospital to administer small doses of antitoxin to positive Schick reactors in Scarlet and Measles Wards when cases of diphtheria occur in such Wards, but to leave the negative reactors alone: 500 units of antitoxin are also invariably given to positive Schick reactors in Scarlet Wards the evening before tonsils and adenoids are removed, while it is a rule to give 1500 units to any positive Schick reactor in these wards who, during convalescence, develops a nasal discharge or speckling on the throat. From whatever of these reasons, at different times numerous individuals have received small doses of antitoxin either after completion of or in the course of immunization with toxin-antitoxin mixtures, and it will be interesting to note the after result of the Schick test. It would also be interesting to follow the antitoxin content of their blood by means of such a test as I have mentioned.

It is also admitted that when antitoxin is in the blood actively, as a result of previous infection or from any other cause, and not passively, the

response to an injection of toxin-antitoxin is probably more rapid.

Children and adults with no antitoxin at all in their blood would appear to react more slowly, as judged by the disappearance of the Schick test, than those who, while undoubtedly Schick positive, yet have probably a small dose of antitoxin in the blood. This would occur especially among groups of individuals with a very high Schick positive rate - as in well to do Schools, etc. - and these individuals therefore, showing not only a high susceptibility as regards numbers but also individually, would react more slowly to active immunization than individuals showing a much lower rate of susceptibility. Slum children who have a low susceptibility rate to diphtheria are more likely to have diphtheria organisms in their throats, stimulating the production of antitoxin, and, among such a population, we would expect the response to immunization measures with mixtures of toxin-antitoxin to be greater. This probably explains the different results obtained in the two groups of children in Tables 20 and 22. Zingher⁽³⁰⁾ has demonstrated this in a school where only 33 per cent. of the children were immune: the susceptibles were immunized and only 25 per cent. of these susceptibles were immune in five months: on the other

hand, in another school with originally 54 per cent . of immunes, the same immunization produced immunity in 41 per cent. of cases, this result being due, no doubt, to the greater degree of active immunity even among Schick positive reactors in the second school.

Different kinds of populations, therefore, have different degrees of susceptibility to diphtheria, as judged by the Schick test, and these populations will react differently to toxin-antitoxin mixtures as regards the degree and rate of the production of antitoxin. This fact may have a great bearing on immunization work among school children, because of the difficulty of immunizing a very susceptible population. To get all the susceptible children of a large city Schick tested and immunized with one course of toxin-antitoxin is a big job, and improved immunizing mixtures are necessary to produce as rapid and sure an immunization as possible.

The immunization results which we have observed are so far very reassuring, while in other fields of work the results have also been satisfactory.

Copeman⁽³¹⁾, O'Brien, Eagleton and Glenny report work done in a residential school among 329 children, among whom an epidemic of diphtheria had occurred. Of 329 children, age group 3-16, 102, i.e. 31 per cent., were positive reactors. Of the 227 children who gave

a negative reaction on being Schick tested, 203 remained in the school 11 weeks later; of these, 201, on being retested, again gave a negative or a negative and pseudo response, thus confirming the decision made two months previously. Two showed themselves positive reactors at the second test. These two children had had antitoxin injected before the first test was made. The 102 children who were Schick positive reactors were inoculated with toxin-antitoxin mixtures.

Local reactions occurred in about a third of the children and, though in some cases the area of local reaction was large, the activities of the children were but little interfered with. Constitutional reactions were slight in all but two children.

Of the 102 children, 99 were schicked 11 weeks later, when two gave an undoubted positive, and the remainder a negative or negative and pseudo reaction.

Dudley⁽³²⁾ reports observations on the distribution of diphtheria in a school of over 1000 boys and on the changes from susceptibility to immunity which occurred during outbreaks of diphtheria. The Schick test was carried out four months after the outbreak of an epidemic and revealed the fact that the new boys, on entering the school, were more susceptible to diphtheria than the boys who had been in the school for

long periods, including the time of exposure to several outbreaks of diphtheria. In the course of three months 32 per cent. of susceptible boys became immune, and in the course of nine months, 92 per cent. of the boys - who developed clinical diphtheria - became immune. Of those immunized, the great majority did not become immune till about eight weeks to three months after immunization.

O'Brien⁽³³⁾, Eagleton, Okell and Baxter report their results in doing over 2700 Schick tests among children. The number immunized was 585, and, of this number, between 85 to 98 per cent. of positive reactors became negative in about three months. No serious reactions after injections of toxin-antitoxin mixtures were observed.

Park⁽³⁴⁾ and Zingher, in their early work, were satisfied that, though a certain number of those immunized became immune in a few weeks, yet immunity did not develop as a rule for some months. They⁽³⁵⁾ later reported (1918) the immunization of children in a large number of institutions. In 1921, Zingher⁽³⁶⁾ stated that during that year he and his workers applied the Schick test to 52,000 children in 44 of the larger schools of New York, and those children who were Schick positive or positive combined were immunized with toxin-antitoxin mixtures. The dose of

toxin-antitoxin was 1.5 c.c. instead of 1 c.c. as previously - two doses being given instead of three. This was done in all but one school, in which 3 c.c. of toxin-antitoxin were given in doses of 1 c.c. each. In this school a Schick retest was made after five months, and it was found that 87.5 per cent. were then negative reactors. (The other children injected showed reactions that were still positive, but were very much fainter than the original injections; a fourth injection of toxin-antitoxin was given to these children.) In the other schools, only two injections of toxin-antitoxin had been given. Two of these schools, located in the more densely crowded portions of the city, showed, when Schicked two and a half months after toxin-antitoxin, 76.1 and 64.5 per cent. negative Schick reactions respectively, while most of the children who continued to give positive reactions showed a much fainter area of redness than in the original test. In many cases the brownish pigmentation of the original positive reaction was still present, and was even much larger at this time than the area of redness of the retest. The fainter reactions in the retest stood out in striking contrast to the strongly positive reactions of children who had received the Schick test for the first time.

In the City Hospital I found this borne out,

particularly in the group of adults and children who received toxoid-antitoxin. The original positive reactions were picked out as very good ones, with extremely marked pigmentation and later desquamation, and it was extremely interesting to watch, in a few who ultimately became negative at five weeks after being injected, how the retest at each week showed less and less pigmentation, until finally there was no area of redness produced at all after injecting the test toxin.

As a result of their work, Zingher, writing in the Journal of the American Medical Association on June 24th, 1922, said that they had come to the conclusion that two doses of 1.5 c.c. were not so effective as three doses of 1 c.c. which were injected at intervals of a week. He found that the immunity response to the same mixture of toxin-antitoxin varied greatly in different groups of children. A preliminary stimulus to the tissue cells in Schick positive children, caused by repeated exposure to infection with the diphtheria bacillus, gave better immunization than among those children whose cells had not been previously stimulated ever so slightly and not sufficiently to produce antitoxin in the circulating blood. He thought that there might be a better immunization if the injections were given two weeks

apart instead of one. He also considered that re-testing should not be done till six months after toxin-antitoxin mixtures had been given, and a second course of two or three injections should be given to those still remaining Schick positive. A few children, he found, failed to develop immunity even when several courses of toxin-antitoxin had been given. The results as regards immunity were satisfactory in that among the school children immunized from 70 to 93 per cent. of children were rendered immune after two courses of toxin-antitoxin injections. He found no danger of anaphylaxis either in repeating the injections of toxin-antitoxin or in giving toxin-antitoxin, even after antitoxin had been given.

Drs Schroeder⁽³⁷⁾ and Park showed the development of antitoxin produced by three doses of mixtures of toxin-antitoxin, having different amounts of toxin, in a large number of children. They pointed out - as in Table below - that using 3 c.c. of toxin-anti-

TABLE 24.

Immunization with T.A.
having different amounts of Toxin.

L + Dose	No. of Children	Per cent. Immune	
.1 L +	490	90	} Reschicked 4 months after T.A.
.5 L +	304	95	
3.0 L +	318	92	
5.0 L +	487	85	

toxin, each c.c. containing 5 L + doses, 85 per cent. of children were rendered immune out of 487 injected, yet using toxin antitoxin which contained in 1 c.c. only .1 L + dose of toxin, no fewer than 90 per cent. were rendered immune four months later out of a group of 490 children immunized, while the local reactions, as mentioned before, were of no account.

Zingher⁽³⁸⁾ also pointed out at the Annual Meeting of the Medical Society of New York in New York City in 1923, the high rate of immunity produced in a series of schools in New York with this new mixture containing only .1 L + dose, pointing out that from 94.0 to 96.0 per cent. of successfully immunized children were excellent results and about as good as could be hoped to achieve with the old type mixture of toxin-antitoxin. Using different mixtures, different results were obtained, and even using the same mixtures, different results were obtained in different schools where the children were drawn from different sections of the city.

Zingher reported also, at the same Meeting, the trial of injections of toxin in small amount to see if they would be successful in producing an active immunity in a large percentage of children, as Schroeder and Park had showed that three doses of a freshly diluted toxin immunized 41 per cent of children

while three doses of an old deteriorated toxin, of which 1 c.c. caused paralysis in a guinea pig, had immunized 70 per cent. Zingher found that fresh diluted toxin, in three doses of 1/10 M.L.D., which is the maximum amount of toxin which can be injected without causing local necrosis in a positive reactor, only immunized 10 out of 30 children, or 33.3 per cent. (1/10 M.L.D. corresponds to the free or under neutralized fraction of toxin in a toxin-antitoxin mixture which produces immunity in 90-95 per cent. of positive reactors.) Zingher assumed, therefore, that the toxin antitoxin mixture contained not only a certain amount of free toxin, but also free toxoid, which is apparently also effective as an agent in stimulating the production of antitoxin. The value of toxoid for immunization purposes has been confirmed, says Zingher⁽³⁹⁾ and Park, by using modified diphtheria toxin, treated by the addition of 0.1 per cent. formalin, according to the suggestion of Glenny and Hopkins. They showed that good results had been obtained at the end of three months in four schools. The diphtheria toxoid was prepared in a special way by their co-worker, Dr Banzhof. The intramuscular injections only caused slight local reactions and no more marked than after the use of the new 1/10 L + mixtures. In a large number of children injected,

the number of immunes varied from 84 to 98 per cent., the results comparing favourably therefore with those produced with 1/10 L+ mixtures where the number of immunes was from 80 to 95 per cent. of injected school children.

Zingher advised the use of the control test when the Schick retest was made to check the immunizing results. He considered that, not only the special mixture used ought to be thought of in judging the results, but also the individual group of children treated, and the time which had elapsed after the injections. The time factor was specially important, immunity developing in due time without further injections being given in cases where a Schick test showed the individual still a positive Schick reactor.

Zingher⁽⁴⁰⁾ reported in 1923 that more than 150,000 children in New York had up to then been given the Schick test. In a communication received from him a few months ago, he points out that he, with a group of assistants, had tested over 350,000 school children in New York and immunized all the susceptible children, and he refers to the new mixture of 1/10 L+ per c.c. He stated that it produced, as far as he could see, very little local or constitutional disturbance. He had personal experience of it among over 3000 children in a suburban town, among well to

do families, and not one of these children had to remain away from school the following day, and, not only were the reactions mild, but the immunity results were excellent. He had noted as high as 95 per cent. successfully immunized children after three doses of this new preparation.

PRACTICAL RESULTS.

Zingher, in a communication to us and referring to the immunization of the thousands of school children in New York, pointed out the reduction in diphtheria incidence and mortality which had taken place,

TABLE 25.

Diphtheria: Incidence and Mortality,
New York, 1919-1923.

Year	Cases	Deaths
1919	14,014	1,239
1920	14,166	1,045
1921	15,110	891
1922	10,427	874
1923	8,050	547

namely, that, as shown in Table 25, the mortality in 1923 had been reduced to less than half what it was two and a half years before.

Peters⁽⁴¹⁾ reports that he tested 212 of the staff of the City Fever Hospital, Bristol, and immunized those susceptible. Among those apparently giving negative Schicks, two developed clinical diphtheria, including himself. Among those inoculated with toxin antitoxin, two developed diphtheria while being immunized, and one two months after completion of the immunizing course. He⁽⁴²⁾ later states that, though he thought that a negative Schick did not always mean complete clinical immunity to diphtheria under the exceptional conditions to which a fever hospital staff are exposed in nursing an unusually virulent type of the disease, it certainly always indicated a comparatively high immunity, and, though a few of the negative Schick reactors developed diphtheria, it was of a very mild type compared to extremely serious attacks from which members of the staff had suffered previous to the adoption of the Schick method. He also stated that, in reference to immunity conferred by toxin-antitoxin mixtures, none of the staff who had had three doses of this mixture had contracted diphtheria over a period of 26 months. With two doses, a few failures of protection were

recorded. He had been giving all new nurses, he went on to say, three doses of toxin-antitoxin before allowing them to nurse in the diphtheria wards, without applying the Schick test to them at all, and up to the present (April 1924) none of the 32 new members of the staff so treated had contracted the disease although daily exposed to a type of disease of high virulence. He was personally convinced that the general use of toxin-antitoxin mixtures in schools would have a profound effect in reducing mortality.

As far as we are concerned, the results in the Edinburgh City Hospital among the staff have been satisfactory.

TABLE 26.

Nurses developing Diphtheria in City Hospital,
Edinburgh.

Years	Number
1919	17
1920	10
1921	14
1922	13
1923	5
1924	

Immunization began in
City Hospital at the
end of September 1922.

Table 26 shows that, while the number of nurses developing diphtheria annually in the Hospital was,

on the average, from 1919 to 1922 inclusive, over 13, this number was reduced to 5 during 1923. Of these, 2 had not been tested; 2, though Schick positive, had not been protected; and 1 had been immunized, and, though noted as negative, had contracted what was, at the worst, a very slight attack of diphtheria.

During this year (1924) five nurses have been warded in the diphtheria pavilion, and of these, one had a positive Schick and had not yet been protected - she had an undoubted but somewhat mild attack of diphtheria -; two were negative Schick reactors who developed mild diphtherias; a reschick in both cases proved them probably slightly positive, with a pseudo; the other two had been immunized over a year. One of them had only a tiny speck on the throat and a previous Schick had proved her still mildly susceptible to diphtheria, while the other had only a very mild diphtheria. She too was probably still slightly susceptible to diphtheria, as her previous Schick, though noted as negative, was probably slightly positive.

During the last two years, three nurses, therefore, out of a total of 132 immunized in the City Hospital, have developed what at the worst was mild diphtheria, and of these, one was no more than a carrier, while the other two were extremely mild cases which convalesced satisfactorily.

Appendix:

Dr Foord Caiger⁽⁴³⁾, in the Annual Report of the Metropolitan Asylums Board, London, for the year 1923-24, tells how, in view of the occurrence from time to time of diphtheria among the boys of the training ship "Exmouth", the Board decided to have their susceptibility to the disease tested and those Schick positive immunized. The work was carried out by Dr O'Brien and his assistants, who reported that the total number of boys tested was 626, a great many of whom had been on the ship for a long time. Of these, 541 or 86 per cent. gave a negative result, showing that they were immune. Of the 85 susceptibles, 77 received immunizing injections, and 8 were not protected. Of the 77, on subsequent retesting - within three months - 66 were found to be immune, and 11 were still positive. The 11 found susceptible were retested a month later, and, of these, 8 were immune, leaving 3 still susceptible. These three boys were retested at intervals till only one was left. He was re-inoculated with toxin-antitoxin and later retested and found negative.

The subsequent work of testing and immunizing new arrivals on the ship was undertaken by two of the assistant medical officers of the Board, who in the same report give their experience of six months prophylactic work on the ship. They report as follows:-

Total number of boys tested	170
" " " negative	96
" " " positive	74

giving 43.5 per cent. susceptible to diphtheria.

Of the 74 susceptible, 62 received three doses of toxin-antitoxin - 1 c.c. each at intervals of a week. They found that 85.5 per cent. of positive reactors became immune, roughly about eight weeks from the date of the first injection.

Six of the 7 failures were re-immunized with three more doses of toxin-antitoxin, and, when retested four weeks later, 5 of them had become negative reactors, and 1 still remained positive. They point out that, whereas O'Brien found only 14 per cent. susceptible among old boys, they themselves found 43.4 per cent. susceptible among the new boys. The old boys were apparently developing immunity through contact with the cases of diphtheria.

SUMMARY OF MAIN CONCLUSIONS.

1. Owing to the very high susceptibility rate to diphtheria, as shown by the Schick Test in a group of over 3,300 individuals, all children from six months to five years should be

immunized against diphtheria with toxin-antitoxin mixtures - 3 c.c. being given at intervals of a week in 1 c.c. doses - without a preliminary Schick test. Owing to the very low susceptibility to Protein, as shown by the few pseudo reactions seen under five years of age, the full course of 3 c.c. can be safely given to these young children. This immunization work of children under five years of age should be carried out either by the family practitioner or at Child Welfare Centres.

2. Owing to the high rate of susceptibility to diphtheria seen also among school children between the ages of 5 and 10, those children who are positive reactors to the Schick test should be immunized with a full course of toxin-antitoxin mixtures.

Owing to the low pseudo rate among these children from 5 to 10 years of age, the control test should be omitted among these children, thus saving time. This means only a few children in every hundred being immunized needlessly, - children who might be negative if a control test were done. This work should

be carried out in the schools with the help of the school staff.

3. Owing to the increasing development of immunity to diphtheria from 10 years onwards, children above this age, and adults, should only be immunized if they are Schick positive, and if they be resident in districts and institutions where they are likely to come in contact with diphtheria, either during the course of epidemics or, as in the case of nurses and doctors in hospitals, in their daily work. The increasing susceptibility to protein renders it necessary to do a control test in all children over 10 years and in adults, in order to avoid giving unnecessary doses of toxin-antitoxin mixtures to a large number of individuals.
4. Accuracy in technique is necessary in doing the Schick test, but the test is easy to perform. Care in reading the results is also necessary, but this presents no difficulty except in the case of those with pseudo reactions.
5. Reactions from the injections of toxin-antitoxin are, as a rule, trivial under 10 years of age; above this age they may become more marked;

but even the worst reaction in the adult rapidly clears up and leaves no ill effects.

6. Rapidly accumulating evidence shows the benefit which immunization with toxin-antitoxin mixtures bring in the shape of lowered morbidity and mortality rates where the procedures have been largely carried out among thousands of school children, as in New York.

The immunity produced by toxin-antitoxin mixtures lasts for a long time. Authorities in America have watched the same individuals for years and believe that such immunity is permanent.

7. In about 7000 Schick tests performed, and in about 3000 injections of toxin-antitoxin given, no harmful results were observed either locally or otherwise.
8. The procedures, therefore, are simple and safe and the results so far reassuring, but the aim ought to be to obtain preparations which will produce a sufficient immunity in as short a time as possible with the fewest number of doses, and with little disturbance to the individual. When these are obtained

Diphtheria, instead of being such a dread disease, especially among children, will be a thing of the past.

REFERENCES.

- (1) Caiger, F. F.: Annual Report, 1923-1924, of Met. Asylum's Board.
- (2) Ker, C. B.: The Annual Report of the Public Health Department for the City of Edinburgh, 1923, by Dr William Robertson, M.O.H.
- (3) Zingher, A.: Amer. Jour. Child. Dis., August 1918, Vol. XVI., pp.83-102.
- (4) Schick, E.: 1908. Kutanreaktion bei Impfung mit Diphtherietoxin. München. med. Wchnschr., 55, 504.
- (5) Schick, E.: 1913. Die Diphtherietoxin-Hautreaktion des Menschen als Vorprobe der prophylaktischen Diphtherieheils-eruminjektion. München. med. Wchnschr., 60, 2608.
- (6) Behring: 1913. Ueber ein neues Diphtherieschutzmittel. Deutsche med. Wchnschr., 39, 873, and Brit. Med. Jour. May 31, 1913.
- (7) Behring: 1914. Aufgaben und Leistungen meines neuen Diphtherieschutzmittels. Berl. klin. Wchnschr., 51, 917; and Brit. Med. Jour., May 16, 1914.
- (8) Leete, H. Mason: The Lancet, 1920, 1., 192.
- (9) Glenny, A. T., Allen, K., and O'Brien, R. A.: The Lancet, 1921, I., 1236.
- (10) Ward, Gladys: Brit. Med. Jour., June 25th, 1921.
- (11) Ker, C. B. and McGarrity, J.: The Lancet, 1924, I., 1101.
- (12) Zingher, A.: Amer. Jour. Child. Dis. 1917, XIII., 247.
- (13) Dickinson, T. E.: Thesis for Univ. Manchester, Manchester: Sherrat and Hughes, 1921.

- (14) Zingher, A.: Amer. Jour. Child. Dis. 1917, XIII., 247.
- (15) Zingher, A.: Jour. Amer. Med. Assoc., 24th June, 1922, Vol.78, pp.1945-51.
- (16) O'Brien, R. A., Eagleton, A. T., Okell, C. C., Glenny, A. T., and Baxter, E. M.: The Lancet, 1922, I., 739.
- (17) Zingher, A.: Jour. Amer. Med. Assoc., Sept. 10, 1921, Vol.77; pp.835, 841.
- (18) Dudley, S. F.: The Schick Test, Diphtheria and Scarlet Fever. A Study in Epidemiology. Med. Research Council, Spec. Report Series, No.75.
- (19) Park, W. K. and Zingher, A.: Jour. Amer. Med. Assoc., Sept. 5th, 1914, and December 18th, 1915.
- (20) Zingher, A.: Amer. Jour. Child. Dis., August, 1918, Vol.XVI., pp.83-102.
- (21) Zingher, A.: Jour. Amer. Med. Assoc., Sept. 10, 1921, Vol.77, pp.835, 841.
- (22) Zingher, A.: New York State Journal of Medicine, Feb. 1, 1924.
- (23) Zingher, A. and Park, W. K.: Proceedings of Soc. for Exp. Biol. and Med., 1924, XXI., pp.383, 385.
- (24) Glenny, A. T., Allen, K., and O'Brien, R.A.: The Lancet, 1921, I., 1236.
- (25) Schroeder, C. H. and Park, W. K.: Jour. Amer. Med. Assoc., Oct. 27th, 1923.
- (26) Zingher, A.: Jour. Amer. Med. Assoc., Sept. 10, 1921, Vol.77, pp.835, 841.
- (27) Kramer, P. H.: Nederl. Jijdschr. v. Geneesh., April 7th, 1923.
- (28) Zingher, A.: Amer. Jour. Inf. Dis., 1916, 19, p.557.
- (29) Zingher, A.: Amer. Jour. Child. Dis., August, 1918, Vol.XVI., pp.83-102.

- (30) Zingher, A.: Jour. Amer. Med. Assoc., 24th June, 1922, Vol.78, pp.1945-51.
- (31) Copeman, S. M., O'Brien, R. A., Eagleton, A. J., and Glenny, A. T.: Brit. Jour. Exp. Path., 3, 42, 1922.
- (32) Dudley, S. F.: The Schick Test, Diphtheria and Scarlet Fever. A Study in Epidemiology. Med. Research Council, Spec. Report Series, No.75.
- (33) O'Brien, R. A., Eagleton, A. J., Okell, C. C., and Baxter, M.: Brit. Jour. Exp. Path., 1923, 4, 29.
- (34) Park, W. K., and Zingher, A.: Jour. Amer. Med. Assoc., Sept. 5th, 1914, and Dec. 18th, 1915.
- (35) Zingher, A.: Amer. Jour. Child. Dis., August, 1918, Vol.XVI., pp.83-102.
- (36) Zingher, A.: Jour. Amer. Med. Assoc., Sept. 10, 1921, Vol.77, pp.835, 841.
- (37) Schroeder, C. H., and Park, W. K.: Jour. Amer. Med. Assoc., Oct. 27th, 1923.
- (38) Zingher, A.: New York State Journal of Medicine, Feb. 1, 1924.
- (39) Zingher, A., and Park, W. K.: Proceedings of Soc. for Exp. Biol. and Med., 1924, XXI., pp.383, 385.
- (40) Zingher, A.: Amer. Jour. Child. Dis., May, 1923. Vol.25, pp.392-405.
- (41) Peters, B. A.: The Lancet, Oct. 6th, 1923.
- (42) Peters, B. A.: The Lancet, April 19th, 1924.
- (43) Caiger, F. F.: Annual Report, 1923-1924, of Met. Asylum's Board.
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