THE NEWER KNOWLEDGE OF DIPHTHERIA AND SCARLET FEVER AND ITS APPLICATION IN HOSPITAL PRACTICE AND IN COMMUNITY IMMUNISATION.

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(With 2 Charts.)

CONTENTS.

I. Introduction.

The newer knowledge of the bacteriology, immunology and serum-therapy of scarlet fever and diphtheria has warranted the following experimental investigation into the control of these diseases in Aberdeen during the past three years. The subject is developed under headings dealing in sequence with etiology, diagnosis, susceptibility tests, prevention by immunisation and antitoxic treatment.

The devising of an intradermal test of susceptibility to diphtheria by Schick (1908) and the use of toxin-antitoxin mixtures for the prevention of the disease as first suggested by Theobald Smith (1907), and as elaborated by Park (1913, 1915), Zingher (1915), and others, opened up a new field for research and provided a fresh prospect of adequately controlling diphtheria.

In the same manner the new light that has recently been thrown on the microbiology of scarlet fever has been a great advance. This fresh prospect of adequately controlling scarlet fever undoubtedly had its principal origin in the fundamental work of G. F. Dick and G. H. Dick (1923, 1924) wherein

https://doi.org/10.1017/S0022172400009177 Published online by Cambridge University Press

these workers demonstrated that a particular variety of toxin-producing streptococcus apparently causes scarlet fever, that the symptoms of the disease are caused by the toxins of this organism, that the tissue cells of a convalescent patient provide a protective antitoxin, and that scarlet fever may be produced by experimental inoculation with haemolytic streptococci and cured with antitoxic serum.

It is true that 43 years ago Loeffler (1884) had directed attention to the haemolytic streptococci which are invariably present in the throats of acutely ill scarlet fever patients, that Marmorek (1895) and Moser (1902) had produced scarlatinal antistreptococcic serums of some potency, that Savchenko (1905) had demonstrated that scarlatinal streptococci produce a potent exotoxin, that Gabritschewsky (1907) had actively immunised children with a scarlatinal streptococcus vaccine, and that Polotevkova (1921) had demonstrated the potency of Gabritschewsky's vaccine; but even with such results available, and in the absence of a measure of the streptococcus toxin such as was devised by the Dicks (1923), the current view of the vast majority of epidemiologists was the view set forth in current text-books such as the third edition of Kolmer, 1923, wherein it is stated "that the virus of scarlet fever is unknown, that those patients who are overwhelmed and prostrated at the very onset are probably intoxicated with the true scarlatinal virus, and that streptococci are probably the most important bacteria of secondary infection."

It has seemed well to emphasise this point since there has been a tendency to minimise the fundamental importance of the work of the Dicks as being merely a step in the ordered progress of the research into the disease. The work of the Dicks was undoubtedly merely a step in the progress of research, and was inspired by consideration of the work of Schick and his collaborators in regard to diphtheria; but a measure of toxicity, viz. the Dick test (Dick, 1924), was essential before the work of the earlier investigators could be corroborated and put on a scientific basis and the new immunising devices made generally available. At the same time it must frankly be admitted that the accumulated data relative to the value of active immunisation against diphtheria by means of a diphtheria toxin-antitoxin mixture enormously stimulated the work on scarlet fever and has provided the prospect of making available a combined diphtheria and scarlatina prophylactic which will be safe and efficient.

In the experimental investigation into the newer methods of actively and passively immunising against diphtheria and scarlet fever, as about to be recorded, the work has been carried out within the in-patient and out-patient departments of Aberdeen City Fever Hospital, within the schools of the Education Authority, and within the City generally.

II. Etiology of Scarlet Fever.

Streptococcus haemolyticus *in Scarlet Fever Cases.* The bacteriological investigation (J. Smith, 1926) has shown that haemolytic streptococci can be

obtained from the throats of practically all cases of scarlet fever during the initial stages of the disease. From 247 cases of scarlet fever on admission to hospital 209 strains of haemolytic streptococci were obtained on culturing the tonsillar secretion, while another strain was obtained from the pus in a case of surgical scarlatina. Table I shows the number of cases in relation to the presence of haemolytic streptococci in the throat culture.

Table I. *Number of cases showing* S. haemolyticus *in throat cultures.*

Day of illness when admitted	1	2	3	4	5 and over
Total number of cases	69	82	47	24	34
Number positive	63	77	36	15	18
Number negative	6	5	11	9	16
Percent. positive	91	93	76	62	52

A preliminary serological classification of these various strains has been accomplished by means of the agglutination and absorption tests. These reactions have shown that the strains of *S. haemolyticus* can be divided into various groups. Type I strains were obtained from 118 cases, Type II strains from 57 cases, and the strains from 34 cases remained unidentified. In addition, the pus from one case of surgical scarlet fever, from which no haemolytic streptococci could be obtained from the throat culture, showed a Type I strain. Different types have not so far been encountered in the throat cultures from cases at the commencement of the illness even though two strains were tested from each source.

From nasal swabs of 247 cases haemolytic streptococci were obtained 16 times. Ten cases showed Type I streptococcus, five cases Type II, and in one case the strain was not classified.

In addition to the case of surgical scarlet fever, pus was obtained from ten cases during the course of the disease, and the relationship of these strains to those obtained from the throat and nose of the same case is shown in Table II.

Table II.

		Serological types isolated		
Case No.	Septic complication	Throat	Nose	Pus
1	Mastoiditis	I	0	II
2	„	I	0	I
3	„	II	0	II
4	Otitis	I	0	I
5	„	II	II	I
6	„	II	0	II
7	Adenitis	II	0	II
8	Otitis	II	0	II
9	Adenitis	+	+	+
		(All strains unidentified)		
10	„	I	0	I

Two to three members of five families were admitted to hospital suffering from scarlet fever and the strains found in the throat cultures have shown agreement in their serological classification, except in one instance, where the second case occurred after the first had been discharged from hospital. Again, two localised outbreaks of scarlet fever in the wards of a hospital showed, in

the first instance, seven cases all harbouring Type I strains and in the second outbreak three cases with Type II streptococcus. Strains of streptococci have also been obtained from various individuals not suffering from scarlet fever, and, of these, four strains from cases of otitis, cervical abscesses, purulent rhinitis, and from a normal throat were found to belong to Type I. Type II strains were obtained from two cases of tonsilitis and from the respiratory passages of four normal individuals in a scarlet fever infected ward.

In the development of this preliminary work on the classification of scarlatinal streptococci it has been found repeatedly that haemolytic streptococci obtained from cases of tonsilitis fall into one or other of the serological groups of the scarlatinal streptococci, and that streptococci isolated from cases of puerperal fever, erysipelas, broncho-pneumonia and the pyogenic infections also fall within the scarlatinal serological groups. The detailed evidence relating to these findings will be submitted in a later contribution, and the findings are referred to here in order to throw light on the nature of the immunity induced by injections of scarlatinal streptococcus toxin and on the increased incidence of streptococcal tonsilitis that has been found to occur in nurses immunised against scarlet fever, to which reference is made in some detail in a later part of the text (see p. 338).

This further investigation fully confirms our earlier finding to the effect that the same type of streptococcus can on occasion originate at least five separate clinically distinguishable diseases, namely, scarlet fever, tonsilitis, erysipelas, puerperal fever, and broncho-pneumonia, and accordingly there emerges what amounts to a new epidemiological conception, and it is necessary to reorientate present knowledge of immunological processes to meet this fresh requirement. From this new viewpoint, therefore, it would appear that, so far as streptococcic infections are concerned, the nature of the resulting disease entity is determined by the toxigenic qualities of the type of streptococcus, by the susceptibility or insusceptibility of the individual as determined by the absence or presence of the specific antibodies in the blood, and by the site of the infection itself.

In a critical review of the various steps undertaken in working out the etiology of scarlet fever, Dochez (1925), who has himself made contributions of the greatest importance to this subject, states that the chain of evidence in favour of the streptococcus is as strong as that in many diseases whose etiology is now accepted without discussion, and that there is little room to doubt that the *S. scarlatinae* is the principal and probably only cause of scarlet fever.

III. Diagnosis of Scarlet Fever.

Schultz-Charlton Reaction. The Schultz-Charlton test (1918) has been carried out among 135 patients, who were in their clinical appearances undoubted cases of scarlet fever.

Reference to Table III shows that the Schultz-Charlton reaction was

positive in 92·1 per cent. of 51 cases that were tested when the rash was at its highest stage of development, and in 88·1 per cent. of 84 cases tested when the rash was beginning to fade. It is not contended, however, that the degree of development of the rash alone determines a positive or negative result. On the contrary, the Schultz-Charlton reaction has on occasion been found negative in patients whose rash was fully developed and of a lobster-red appearance. Experience has satisfied us that, while the Schultz-Charlton reaction is of real assistance in the diagnosis of doubtful cases of scarlet fever, its

Table III.

Rash at its height			Rash commencing to fade		
No. tested	No. positive	Percentage positive	No. tested	No. positive	Percentage positive
51	47	92·1	84	74	88·1

value is greatly limited by the impossibility of obtaining a definite reading with rashes other than those that are at the height of their development.

The Dick test of susceptibility to scarlet fever is of some value in diagnosis, but the value is limited. Thus, as shown in Table IV, 86·3 per cent. of scarlet fever patients have been found to give a positive Dick reaction during the first two days of illness, after which the percentage of positive reactors steadily diminishes; but a Dick-positive reaction has its use as a confirmatory test in the presence of a positive Schultz-Charlton reaction. A Dick-positive reactor becomes negative within 24 hours of antistreptococcic serum administration.

IV. SUSCEPTIBILITY TESTS TO SCARLET FEVER AND DIPHTHERIA.

(*a*) *Dick Test of Susceptibility to Scarlet Fever.*

The results of a preliminary investigation (Smith and Taylor, 1926) of the value of the Dick test as a measure of susceptibility to scarlet fever have already been published and are in accord with those obtained by American workers. These preliminary tests are summarised in Table IV.

Table IV. *The Dick Test in Scarlet Fever Patients.*

Day of disease	1–2	3	4	5	6	7–14
Total number tested	58	40	30	17	7	18
Number positive	50	28	18	9	3	5
Number negative	8	12	12	8	4	13
Percent. positive	86·3	70	60	52·9	42·8	27·7

Thus of 170 cases of scarlet fever tested, 86·3 per cent. gave a positive Dick reaction in the first two days of the illness. The percentage of positive reactors rapidly decreased, and when 158 were retested during convalescence in the fourth week of the disease, only 14 per cent. were found to react positively. Of 267 normal individuals who gave no history of scarlet fever, and who were Dick-tested, it was found that in the age period under 6 months only 20 per cent. gave a positive reaction; from 6 months to 5 years, 77 per

cent. gave a positive reaction; in the 6–10 year period, 46 per cent.; in the 10–20 year period, 38 per cent.; while in the group 20 years and upwards, 27 per cent. still gave a positive Dick reaction. In a series of 60 individuals who gave a definite history of having had scarlet fever, and who consisted for the most part of the nursing and domestic staff of the hospital, 9 individuals gave a positive Dick reaction.

This preliminary investigation having been completed, we proceeded to elaborate the work, and with this end in view we determined the varying susceptibility of the patients in hospital, of children attending middle-class and west-end schools, of children attending the various Child Welfare Centres, and of adults throughout the City generally.

Susceptibility to Scarlet Fever according to Age-period. Table V shows the results, in age-groups, of the Dick test carried out in 1500 individuals of random distribution, the individuals being tested without regard to class, occupation, locality, size of dwelling, previous attack of the disease, or any other factor which apparently may have an influence on susceptibility.

Table V. *The Dick and Schick Test in* 1500 *Individuals* (*normal*).

(The signs + and − denote positive and negative throughout the tables.)

Age groups	Nos. Dick-tested and Schick-tested	Percentage Dick +	Percentage Schick +	Percentage Schick and Dick +	Percentage Schick and Dick −
0– 5 years	63	96·4	94·0	90·4	4·0
5–10 ,,	602	81·2	80·0	67·2	5·2
10–15 ,,	664	65·5	67·9	51·7	13·2
15–20 ,,	119	60·8	64·5	47·4	13·9
20–25 ,,	44	52·4	54·2	35·6	26·9
25 years and over	8	27·2	27·2	18·1	19·1
Total Nos.	1500*	72·1	73·0	58·6	10·9

* Including 121 persons who had formerly suffered from scarlet fever and of whom 13, or 10·7 per cent., proved Dick-positive. The figure also includes 105 persons who had previously suffered from diphtheria, and of whom 43, or 41·0 per cent., were Schick-positive.

Reference to the table shows that in the age-period 0–5 years, 96·4 per cent. gave a positive Dick reaction; 5–10 years, 81·2 per cent. gave a positive reaction; 10–15 years, 65·5 per cent. were positive; 15–20 years, 60·8 per cent.; 20–25 years, 52·4 per cent.; and 25 years and over, 27·2 per cent.

Susceptibility to Scarlet Fever according to Sex. Table VI shows the results,

Table VI. *Susceptibility in the Sexes.*

Age groups	Nos. Dick-tested and Schick-tested	Percentage females Dick +	Percentage males Dick +	Percentage females Schick +	Percentage males Schick +
0– 5 years	63	92·1	95·6	96·8	83·3
5–10 ,,	602	79·6	83·4	80·6	81·5
10–15 ,,	664	64·8	68·2	74·4	65·1
15–20 ,,	119	73·1	47·4	88·5	68·4
20–25 ,,	44	62·5	52·4	75·0	47·6
25 years and over	8	—	—	—	—
Total Nos.	1500	66·9	50·2	85·5	63·7

in males and females respectively, according to age-period, of the Dick test carried out in the same 1500 individuals.

On referring to Table VI, it is found that, in the 0–5 year age-period, 95·6 per cent. of males are Dick-positive as compared with 92·1 per cent. of the females; in the 5–10 year age-period, 83·4 per cent. males to 79·6 per cent. females; in the 10–15 year age-period, 68·2 per cent. males to 64·8 per cent. females; in the 15–20 year age-period, 47·4 per cent. males to 73·1 per cent. females; and in the 20–25 year age-period, 52·4 per cent. males to 62·5 per cent. females.

Susceptibility to Scarlet Fever according to Social Condition. Table VII shows the results of susceptibility according to social condition. In this connection, 718 children from west-end schools have been tested, 392 children from middle-class schools, and 404 children from east-end schools.

Table VII. *Susceptibility according to Social Condition.*

Dick test			Schick test		
Nos. tested	No. Dick +	% Dick +	Nos. tested	No. Schick +	% Schick +
		West-end school children			
718	562	78·3	708	556	78·5
		Middle-class school children			
392	231	59·0	376	235	62·5
		East-end school children			
404	118	29·2	404	126	31·2

It is found that, of west-end school children, 562, or 78·3 per cent., were Dick-positive; of middle-class school children, 231, or 59·0 per cent., were Dick-positive; while of east-end school children, 118, or 29·2 per cent., were Dick-positive.

Susceptibility to Scarlet Fever of Persons who gave a History of having formerly suffered from the Disease. It next appeared desirable to ascertain the susceptibility to scarlet fever as determined by the Dick test of persons who had formerly suffered from scarlet fever. Reference to foot-note to Table V (see p. 332) shows that of 121 persons who had formerly suffered from scarlet fever, 13 individuals, or 10·7 per cent., proved Dick-positive.

The Dick Susceptibility Test in Cross-infected Wards. Further evidence of the value of the Dick test as a guide to the susceptibility of individuals has also been obtained by testing patients in wards in which cross-infection with scarlet fever has taken place, or in wards to which cases of scarlet fever may have been accidentally admitted. In this way scarlet fever has been observed to occur in 21 patients who previously showed a positive Dick reaction. On the other hand, numerous cases (notified as scarlatina) were admitted to the scarlet fever wards with no definite clinical sign of the disease and when found to be Dick-negative were allowed to remain in contact with other scarlet fever cases. In no single instance was a case of scarlet fever found to follow. In seven instances, cases were admitted in the third or fourth week of illness

with definite desquamation and appeared clinically to have had a typical attack of scarlet fever. The Dick test in all seven cases was markedly positive on admission, and all developed a second attack of the disease. In those cases in which the Dick test had been carried out during a period of two to three weeks prior to the attack of scarlet fever the area on the forearm corresponding to the previous reaction again became intensely red as compared with the rash on the surrounding skin.

Observation. It has been observed that the intensity of the Dick reaction is of much significance, and in the present investigation scarlet fever has only been found to occur in individuals giving a marked Dick reaction. It is thus probable that numerous individuals regarded at present as susceptible will later be eliminated when further investigation has been made of the immunity mechanism in scarlet fever and when a method of more accurate standardisation of the toxin has been evolved. The future, however, will undoubtedly see the Dick test in relation to scarlet fever as firmly established as the Schick test is in relation to diphtheria.

(*b*) *Schick Test of Susceptibility to Diphtheria.*

The results of the Schick test as here recorded are in the main in conformity with the results obtained in America and elsewhere.

Susceptibility to Diphtheria according to Age-period. Schick tests were performed in the 1500 individuals, the results of whose Dick tests have been recorded above, and it has been seen that these individuals were tested without regard to class, occupation, locality, size of dwelling, previous attack of the disease, or any other factor which apparently may have an influence on susceptibility. Reference to Table V on p. 332 shows that in the age-period 0–5 years, 94·0 per cent. gave a positive Schick reaction; in the age-period 5–10 years, 80·0 per cent. gave a positive reaction; in the 10–15 years age-period, 67·9 per cent.; 15–20 years, 64·5 per cent.; and 20–25 years, 54·2 per cent. The figures for the later age-periods are too small to have any statistical value.

Susceptibility to Diphtheria according to Sex. Table VI (see p. 332) shows the results in males and females respectively, according to age-period, of the Schick test carried out in the same 1500 individuals, and in the table the result of the Dick and Schick tests can be readily contrasted. It is found that, in the 0–5 years age-period, 83·3 per cent. of males were Schick-positive as compared with 96·8 per cent. of females who were Schick-positive. In this age-period, however, the numbers are too small to provide reliable data. In the 5–10 years age-period, 81·5 per cent. of males as compared with 80·6 per cent. of females; in the 10–15 years age-period, 65·1 per cent. males to 74·4 per cent. females; in the 15–20 years age-period, 68·4 per cent. males to 88·5 per cent. females; and in the 20–25 years age-period, 47·6 per cent. males to 75·0 per cent. females. In this age-period the numbers are again too small to provide reliable data.

Susceptibility to Diphtheria according to Social Condition. Table VII (see p. 333) shows the results of susceptibility to diphtheria according to social condition, as contrasted with susceptibility to scarlet fever. In this connection, 708 children from west-end schools have been tested, 376 children from middle-class schools, and 404 children from east-end schools. It is found that, of west-end school children, 556, or 78·5 per cent., were Schick-positive; of middle-class school children, 235, or 62·5 per cent., were Schick-positive; while, of east-end school children, 126, or 31·2 per cent., were Schick-positive.

Susceptibility to Diphtheria of Persons who gave a History of having formerly suffered from the Disease. Some 105 persons who had previously suffered from diphtheria have also been Schick-tested, and reference to foot-note to Table V (see p. 332) shows that 43 of these, or 41·0 per cent., were Schick-positive. It was also observed that the Schick reaction in the majority of these positive cases was less intense than in individuals who had not suffered from diphtheria.

The Schick Susceptibility Test in Cross-infected Wards. The Schick test has also proved of the utmost value as a guide to the susceptibility to diphtheria of nurses and patients in wards in which cross-infection with diphtheria has taken place or in wards to which cases of diphtheria may be accidentally admitted. Thus, all patients on admission to the scarlet fever wards are immediately Schick-tested, and if a case of diphtheria has recently occurred in the ward then all positive Schick reactors can be protected by a passively immunising dose of diphtheria antitoxin.

The experience has been that Schick-negative reactors can be left in contact with doubtful cases of diphtheria, or even with actual cases of the disease, without contracting diphtheria. Not infrequently it has been necessary, owing to lack of isolation accommodation, to leave in the scarlet fever ward a scarlet fever patient who is also suffering from diphtheria or is a diphtheria carrier, and it has been found possible to prevent cross-infection by the comprehensive use of the Schick susceptibility test and passive immunisation of positive reactors as above indicated.

A measure of the effects of this diphtheria prophylaxis can be obtained by comparing the incidence of diphtheria in scarlet fever patients admitted to the City Hospital, on the one hand, with the incidence of diphtheria in the patients admitted to the Royal Hospital for Sick Children, on the other hand. It is found that, in all, 8 cases of diphtheria were notified as occurring among the 1179 scarlet fever patients admitted from January, 1925, to September, 1926, to the City Fever Hospital, where preventive measures were in force, whereas 42 cases of diphtheria were notified as occurring in the Royal Hospital for Sick Children, where a total of 1869 cases were treated during the period mentioned. In other words, 0·7 per cent. of cases of diphtheria occurred among the scarlet fever patients in the City Hospital, as contrasted with 2·2 per cent. of cases of diphtheria in the patients in the Royal Hospital for Sick Children, and it is notorious that scarlet fever patients are particularly susceptible to diphtheria. Not only so, but all of these

8 diphtheria cases as appearing in scarlet fever patients at the City Hospital occurred within four days of admission of the scarlet fever patients, and prior to the readings of the positive Schick tests and the administration of diphtheria antitoxin.

V. Prevention of Scarlet Fever and Diphtheria by Immunisation.

(*a*) *Prevention of Scarlet Fever by Active Immunisation.*

Scarlatinal Streptococcus Toxin. In all the experiments here recorded, the unmodified toxin as prepared in our own laboratories has been used for immunising purposes, severe reactions being eliminated by the employment of three graduated doses of the toxin injected at weekly intervals, the first injection consisting of 500 skin doses, the second of 1000 and the third of 3000 skin doses. The injections are made subcutaneously into the upper arm about the insertion of the deltoid muscle. It has been found that in children under six years of age the reaction produced by such injections is negligible. It has also been found that the immunity to scarlet fever, as judged by a negative Dick reaction following on the streptococcus toxin injections, develops much more rapidly than the immunity to diphtheria following on toxoid-antitoxin injections—the immunity to scarlet fever commonly appearing two weeks after the third injection.

Active Immunisation against Scarlet Fever of Nursing Staff of City Hospital. Since June 1st, 1925, the nursing staff of the City Hospital have been actively protected against scarlet fever before being admitted for duty to the scarlet fever wards. Reference to Table VIII shows that of 122 nurses Dick-tested, 32, or 26·2 per cent., were susceptible to scarlet fever, as indicated by a Dick-positive reaction; and of 29 maids Dick-tested, 7, or 24·1 per cent., were found Dick-positive.

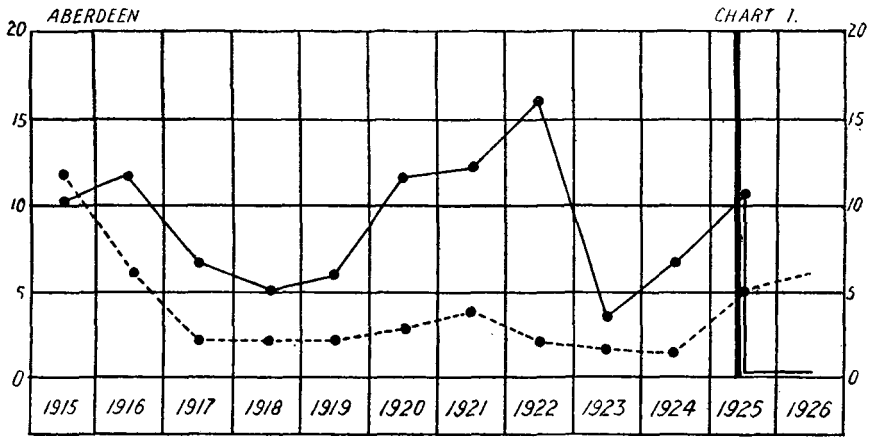
Table VIII. *Dick Test and Immunisation against Scarlet Fever. From June 1st, 1925 to September 30th, 1926.*

Number of nurses Dick-tested			122
,, ,, immunised up to present date ...			32
,, maids Dick-tested			29
,, ,, immunised			7
Results of Dick tests	Nurses...32 +	=	26·2 %
	Maids ... 7 +	=	24·1 %

The 32 nurses found to be susceptible to scarlet fever, as indicated by a positive Dick reaction, received a first series of three immunising injections of scarlatinal streptococcus toxin at intervals of a week, and on re-testing the 32 nurses three weeks after the third injection, 29 were found to be Dick-negative, 2 were definitely Dick-positive, and 1 faintly positive. These three last-mentioned nurses received a second series of immunising injections, and on re-testing three weeks later, all were Dick-negative. Of the 7 maids who were found to be susceptible to scarlet fever, 6 received one series of three immunising injections at intervals of a week, and all 6 were found to

be Dick-negative on re-testing one month later. The remaining maid, who had been found to be Dick-positive, received only one injection of 500 skin doses of toxin, since following this injection she developed a condition indistinguishable from scarlet fever 24 hours later, and following on the illness she was found to be Dick-negative. On re-testing these nurses and maids in September, 1926, all of them were Dick-negative.

Effect of Active Immunisation in Prevention of Scarlet Fever in City Hospital Staff. With regard to the occurrence of scarlet fever in the 122 nurses and 29 maids who have been Dick-tested since June 1st, 1925, and of whom 32 nurses and 7 maids were found to be Dick-positive and were not put on duty in the scarlet fever wards until they had been protected, there has been no case of scarlet fever. The figures are represented in Chart No. 1.



SCARLET FEVER—Attack Incidence per 100 individuals in Staff of City Hospital

" " per 1000 of population

NOTE—Active immunisation against Scarlet Fever was commenced in July, 1925. The total number of individuals (nurses and maids) on the staff of the City Hospital may be put at 125. The disease was in epidemic form in 1921 and 1925–1926.

It is very remarkable that during the 10 years when the case-incidence of scarlet fever per 1000 of the population reached as low a level as 1·2, as in 1924, and during which 10 years the case-incidence of scarlet fever in the nursing and domestic staff never reached a lower level than 4 per cent. of the staff, as in 1923, and reached as high as 16 per cent. of the staff in 1922, nevertheless in 1925, with a case-incidence of 4·5 per 1000 of the population suffering from scarlet fever and with a daily average in hospital of 58 cases, coincident with the active immunisation of the staff, scarlet fever disappeared in the staff. These figures relating to the actual protection of the nursing staff against scarlet fever afforded by active immunisation provide the only statistical data that are yet available in the immunising campaign, and it will be obvious that it is much too early to dogmatise in the matter; but the

figures are very encouraging, and since the hospital draws a large proportion of its nursing staff from rural areas, and since the inhabitants of rural areas are on the whole more susceptible to scarlet fever, the effect of active immunisation on the nursing staff is subject to this wider interpretation.

It has been found, however, that coincident with the disappearance of scarlet fever in the immunised nursing staff of the City Hospital, there has been a notable increase in the incidence of streptococcal tonsilitis in these immunised nurses. Thus, in the decennium of 1916–1925 there was an annual average of 11 cases of tonsilitis in the 95 nurses comprising the nursing staff, or a case-incidence of 11·6 per cent., whereas in the year October, 1925, to September, 1926, the number of cases was 25, or 26·3 per cent. It has been shown that an annual average of 9 cases, or 9·5 per cent., contracted scarlet fever in the City Hospital, and, if this number is subtracted from the 25 cases of tonsilitis, it leaves an average annual number of 16 nurses suffering from tonsilitis, or 16·8 per cent. In other words, the increased incidence of tonsilitis in the nursing staff during this period of the epidemic prevalence of scarlet fever may be wholly explained if it be assumed that such an immunity as is induced by injections of the exotoxin of *S. scarlatinae* fails to protect the immunised nurses from tonsilitis due to this streptococcus. The streptococci obtained from these tonsilitis cases in nurses commonly fall into one or other of the serological groups of scarlatinal streptococci, and it would appear therefore to be proved that the immunised nurses, while protected by immunisation from the toxic effects of the exotoxin of *S. scarlatinae*, are in no wise protected against tonsilitis due to this streptococcus (see p. 340 for further discussion of this problem).

Active Immunisation against Scarlet Fever of Patients admitted to Hospital with Diphtheria. On the admission of all cases of diphtheria to hospital, sanction is obtained to provide active immunisation against scarlet fever for these patients, and all such patients are Dick-tested on admission. It has not been found practicable, however, to proceed with the active immunisation of the Dick-positive reactors while in hospital, because the scarlatinal prophylactic produces an erythema in 3 per cent. of the individuals immunised, this erythema introducing a serious difficulty in the differential diagnosis of the rash due to toxin, of serum rash, and of the rash of scarlet fever. It is better, therefore, to postpone the active immunisation of the Dick-positive reactors among the diphtheria patients until after they are discharged from hospital.

Active Immunisation of School Children against Scarlet Fever. After five months' experience of the apparently effective protection provided to the City Hospital nurses by active immunisation against scarlet fever, it was considered that the results justified a wider application of this preventive procedure, and, accordingly, in November, 1925, sanction was obtained from the Education Authority to provide active immunisation against scarlet fever to school children. In all, 303 school children have, to the end of September, 1926, received a first series of immunising injections of the scarlatinal prophy-

lactic. Of these 303 children, 257 were re-tested within four months of receiving the first series of injections, and of these, 194, or 75·6 per cent., were found protected, as indicated by a negative Dick reaction. None of these 194 protected children subsequently contracted scarlet fever, though the disease has been rife in the schools. *One* child, two months after having received a first series of injections, not having been re-tested in the interim, developed scarlet fever.

Prevention of Return Cases of Scarlet Fever. The problem of the return case of scarlet fever was apparently insoluble until active immunisation became possible. Thus, since the beginning of hospital isolation of scarlet fever, patients have been discharged from hospital apparently well, and, within a few days to a month of their return home, have originated fresh cases of scarlet fever. It is true that many of these apparently clean discharged cases that originated return cases were, on later examination, found to be suffering from discharges of one kind or another, but it has been the experience of every one associated with fever hospital practice that on occasion, the convalescent patient, discharged from hospital without any discharge whatsoever and apparently free from all infection, has originated fresh cases.

It occurred to us that active immunisation against scarlet fever might profitably be employed for the protection of all susceptible members of the families to which scarlet fever convalescents were discharged from hospital. We accordingly took steps to have every family, from which a case of scarlet fever had been removed to hospital, visited within 24 hours, and all the remaining members of the family Dick-tested. The results of these Dick tests are noted after 12 hours, and all positive reactors are given a first immunising injection of 500 skin doses of scarlatinal streptococcus toxin, 5 days later a second injection of 1000 skin doses, and 5 days later a third injection of 3000 skin doses, and, within 14 days of the third injection (that is 24 days after the case of scarlet fever had been removed to hospital), these susceptible contacts are found, in the great majority of cases, to be immune, as judged by a negative Dick reaction. Accordingly, when the scarlet fever patient is discharged from hospital, he returns home to a family, the susceptible members of which have all been immunised against scarlet fever.

Up to the end of September, 1926, some 470 families have been visited, and arrangements made with 134 of the families to have the susceptibility tests and necessary immunising injections provided by the family doctor. In 84 out of the 470 families, the patient admitted to hospital was an only child. The members of the remaining 252 families have been tested and immunised under the supervision of the Health Department. The results of the Dick tests, as already recorded, indicate that it is unnecessary to Dick-test children under 6 years of age, since 96·4 per cent. of such children are Dick-positive; and, accordingly, it has been possible to actively immunise without preliminary testing 277 children in the 252 families. An additional 233 children over 6 years of age in these families have been Dick-tested, and of these, 154,

or 66·1 per cent., have been found positive, and these positive reactors have been similarly actively immunised against scarlet fever.

It is interesting to note that, up to the time of reporting, only one return case of scarlet fever has occurred in the 252 families which have been thus protected. During the quinquennium 1921–1925, an annual average of 439 cases of scarlet fever were notified, an annual average of 369 cases were admitted to hospital, and these hospital admissions on discharge caused an annual average of 22 return cases, or 5·9 per cent. of admissions. During the period August, 1925, to September, 1926, 1027 cases of scarlet fever have been notified; 661 cases from non-immunised households have been admitted to hospital where they received serum treatment; and these on discharge have caused 13 return cases, or 2·0 per cent. of admissions; while 252 cases from households which were immunised while the patients were in hospital, have similarly received serum treatment in hospital, and these on discharge have caused 1 return case, or 0·4 per cent. of admissions. The contrast, therefore, is that among the non-immunised families, from 2·0 per cent. to 5·9 per cent. of scarlet fever admissions on discharge have caused return cases, whereas the discharge of 252 cases to immunised households has produced 0·4 per cent. of return cases.

Control of Epidemic Prevalence of Scarlet Fever by Active Immunisation. The results already recorded of the Dick test for susceptibility, of actively immunising and re-testing susceptible individuals, indicate that in about 95 per cent. of cases the Dick-positive reactors become Dick-negative a fortnight after the third immunising injection, although this Dick-negative reaction may not be permanent. Therefore, the immunity to scarlet fever induced by streptococcus toxin develops much more rapidly than that to diphtheria induced by diphtheria toxoid-antitoxin injections. With diphtheria six weeks to six months are needed for immunity to develop. With scarlet fever the period required is much shorter, consequently the prospect of promptly checking the extension of the disease is hopeful. Toxoid-antitoxin injections fail to control epidemics of diphtheria immediately. In the immunising campaign which is being undertaken in Aberdeen, epidemic control of scarlet fever is being attempted, but obviously it will take a considerable time to collect statistics for publication.

(*b*) *The Exotoxin of S.* scarlatinae *and its Detoxification.*

The exotoxin of *S. scarlatinae* used in this investigation has been obtained by growing a strain thereof in Hartley's trypsin broth for 24 hours. Various types of Chamberland, Berkfeld, and Seitz filters have been employed to obtain the germ-free soluble exotoxin with uniform success. The toxin has been standardised by comparing the reactions produced by various dilutions of the new toxin with the reaction produced by the diluted standard toxin on normal children, on acute cases, and on convalescent cases of scarlet fever. The actual Dick-test dose varied between 0·2 c.c. of 1 in 1000 dilution of one

toxin to 0·2 c.c. of a 1 in 2000 dilution of another. As already indicated, graduated doses containing 500, 1000, and 3000 such skin-test doses have been used for producing active immunity. This scarlet fever toxin in the doses indicated produces in certain individuals marked local and general disturbances. Within 24 hours of injection, local redness with swelling of the arm appears, while in very markedly susceptible individuals, general symptoms may develop within a few hours. These consist of fever, vomiting, and exanthem varying from slight erythema to a typical scarlatiniform rash. Except in very exceptional cases, the whole of the symptoms disappear within 24 hours. The reactions appear most frequently after the first dose, and much less frequently after the second. *In exceptionally susceptible individuals, however, it has been repeatedly found that the whole clinical picture of scarlet fever going on to marked desquamation is produced by the subcutaneous injection of the exotoxin derived from the* S. scarlatinae. This phenomenon is well known to the general medical practitioners of Aberdeen who have been taking part in the immunising campaign, but it may not be fully appreciated by those who have merely been following the literature on this subject.

Clearly the most urgent requirement of the present campaign is the production of a detoxified scarlatinal streptococcus toxin or toxoid for immunising purposes so that immunisation is induced with fewer doses, intensifying the immunity produced and so making it more enduring, and eliminating the local and constitutional reactions that the unmodified toxin produces. The unmodified toxin, as used in the experiments already described, produces a scarlatinal erythema indistinguishable from the rash of scarlet fever in 3 per cent. of the persons inoculated. Accordingly, a streptococcus toxin detoxified with 2 per cent. sodium ricinoleate, in accordance with the method of Larson, Evans and Nelson (1924), has been prepared, and attempts have been made to confer immunity with one inoculation of 2000 to 4000 skin doses of this soap mixture to two groups of three children in hospital, these children having previously proved Dick-positive. The result is recorded in Table IX. None of these children had previously suffered from scarlet fever.

Table IX.

			Dick test			Prophylactic		Reactions		Dick re-test. Skin doses			
			Date 1925			Amount	Date 1925		General				
Initials	Age	Sex	Nov.	+	−	S.D.	Nov.	Local	° F.	1	5	10	20
J. M.	3½	M.	18th	+ +	Nil	2000	20th	Nil	Nil	−	+	+	+
C. C.	5	M.	,,	+ +	,,	,,	,,	Slight	,,	−	+	+	+
J. B.	2½	M.	,,	+ +	,,	,,	,,	Nil	,,	−	+	+	+
J. B.	5	M.	,,	+ +	,,	4000	,,	Slight	99·4	−	−	+	+
G. D.	3½	M.	,,	+ +	,,	,,	,,	Nil	99·2*	−	−	+	+
G. B.	4	M.	,,	+ +	,,	,,	,,	Slight	99·0*	−	−	+	+

* Slight rash.

Table IX shows that the three children who each received an injection of 2000 skin doses, when Dick-tested two months later, were negative to

1 skin dose but positive to 5, 10 and 20 skin doses; while the three children who had received 4000 skin doses as a single injection, and who had reacted with a slight elevation of temperature and an evanescent erythematous rash, were negative to 1 and 5 skin doses but positive to 10 and 20 skin doses.

In the present state of the bacteriological investigation, however, we have not been prepared to make use of this soap toxin mixture in out-patients, since there is a possible danger that the ricinoleate wraps round or absorbs the toxin only temporarily, and that the whole of the toxin may under certain circumstances again be released. There is no serious danger in experimenting with such special toxin mixtures in in-patients, since were symptoms of intoxication to appear, they could be immediately neutralised by the exhibition of antistreptococcic serum. As a control to the experiment recorded in Table IX, 4000 *skin doses of untreated scarlatinal streptococcus toxin have been injected into a volunteer medical student, with the result that in* 24 *hours he had a punctate erythema, scarlatinal tongue and throat; in short, his condition was indistinguishable from clinical scarlet fever. In ten days' time he desquamated, and two months later he was found to be Dick-negative.*

It is obvious, therefore, that the whole symptomatology of scarlet fever is due to the action of the exotoxin of *S. scarlatinae*. That this is so, and that the symptoms are not produced by a filterable living virus which might be associated with the filtered exotoxin, is proved by the fact that the filtrate containing the exotoxin is still capable of producing the whole symptomatology of scarlatina in susceptible individuals after the filtrate has been heated to 55° C. for one hour. It further follows that, in producing active immunity by doses of *S. scarlatinae* toxin, the immunity conferred prevents only the effects produced by the exotoxin alone, and has no effect in preventing infection by the scarlatinal streptococcus.

As already indicated, we have not felt justified in making any extended application of the scarlatinal toxin modified by sodium ricinoleate for purposes of immunisation, since experiments on laboratory animals with diphtheria toxin detoxified with sodium ricinoleate have seemed to justify the view that the ricinoleate absorbs the toxin only temporarily, and that the whole of the toxin may, in certain circumstances, be abruptly released. Accordingly, attention has been concentrated on making available a streptococcus anatoxin by modifying the toxin by treatment with formalin. Greater difficulty has been experienced in converting scarlatinal toxin into toxoid than with diphtheria toxin, but a potent non-irritant anatoxin which, it is hoped, will profoundly facilitate the immunising campaign against scarlet fever, has been prepared. The results of this investigation will be published in due course.

(*c*) *Prevention of Diphtheria by Active Immunisation.*

Diphtheria Toxoid-Antitoxin. Toxoid-antitoxin mixtures have replaced the various mixtures of toxin and antitoxin which were previously used for producing immunity to diphtheria. "Toxoid," which has now superseded

"toxin" for purposes of immunisation, is defined as toxin so modified that it no longer possesses its poisonous properties, the change being brought about by exposing toxin to the action of 0·5 per cent. formalin at 37° C. for about four weeks. It has been found that the antigenic or immunising properties of the toxoid are much superior to those of the original toxin. In practice it has not been found possible to convert the last trace of toxin into toxoid. A small amount of antitoxin (27 units) is therefore added to 20 c.c. of toxoid. The mixture is then diluted ten times, and 1 c.c. is used as the dose for producing immunity.

Active Immunisation against Diphtheria of Nursing Staff of City Hospital. Since January 1st, 1922, the nursing staff of the City Hospital have been actively protected against diphtheria before being admitted for duty to the diphtheria wards. Active immunity to diphtheria takes from six weeks to six months to develop after the immunising injections have been given, and accordingly, in order to prevent diphtheria in the City Hospital nurses, it was necessary to make arrangements to Schick-test all nurses on admission, and to arrange that the Schick-positive reactors would be confined to duty in the tuberculosis wards and scarlet fever wards (and, in the latter case, only when they had been protected against scarlet fever) for a period of six months or until such time as the re-tests following the series of immunising toxoid-antitoxin injections showed that the Schick-positive reactors had become Schick-negative. Reference to Table X shows that of 126 nurses Schick-tested, 50, or 39·7 per cent., were susceptible to diphtheria as indicated by Schick-positive reaction; and of 30 maids Schick-tested, 11, or 36·7 per cent., were found Schick-positive.

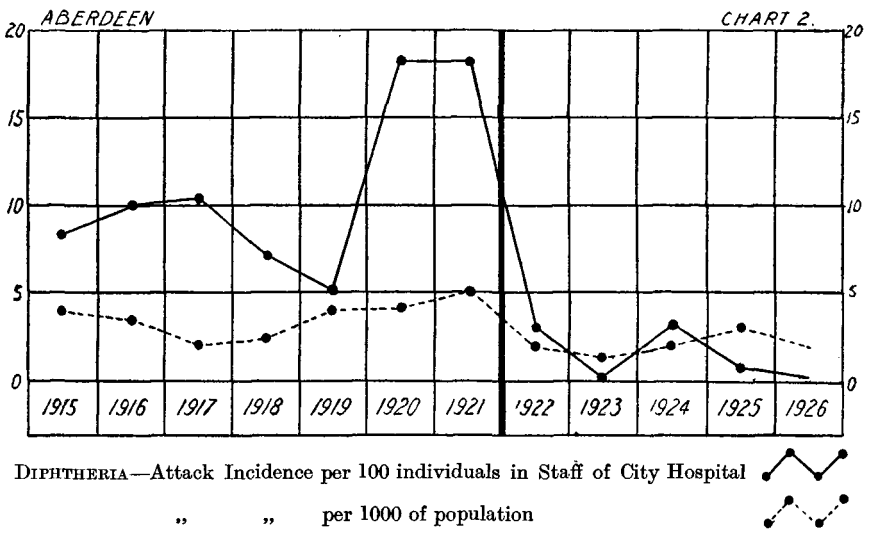
Table X. *Schick Test and Immunisation against Diphtheria. From January 1st, 1922 to September 30th, 1926.*

Number of nurses Schick-tested		126
,, ,, immunised up to present date ...		47
,, maids Schick-tested		30
,, ,, immunised		10
Results of Schick tests	Nurses...50 + =39·7 %	
	Maids ...11 + =36·7 %	

Immunising injections were given to the 50 Schick-positive reacting nurses. Of these, 42 nurses receiving one series of three injections of toxoid-antitoxin mixtures were found to be Schick-negative six months after they had received the injections, while 5 nurses who had received a first series of injections were still Schick-positive after six months. A second series of immunising injections to these 5 nurses resulted in their becoming Schick-negative when tested six months later. The remaining 3 nurses received only one immunising injection on account of the severity of the protein reaction. Since these severe reactions were encountered, it has been possible to immunise even these three nurses by initiating their protection afresh by repeated injections of small amounts of the toxoid-antitoxin mixture, beginning with one-tenth of a cubic centimetre. Of the 11 maids who have been found Schick-positive, 9 were

found to be Schick-negative six months after one series of toxoid-antitoxin injections. One maid required a second series of injections before becoming negative, and one maid received only one injection of toxoid-antitoxin, and was not immunised on account of the severity of the protein reaction.

Results of Active Immunisation in Prevention of Diphtheria in City Hospital Staff. With regard to the occurrence of diphtheria in the 126 nurses and 30 maids who have been Schick-tested since January 1st, 1922, and of whom 50 nurses and 11 maids were found to be Schick-positive and were not put on duty in the diphtheria wards until they had been protected, there have been in all 7 cases of diphtheria during the four years. This demonstrates the remarkable efficacy of the diphtheria prophylactic. Thus, during the seven years 1915–1921, an annual average of 12·4 nurses, or 14 per cent., contracted diphtheria in the City Hospital; and an annual average of 1·3 maids, or 4 per cent., similarly contracted diphtheria in the City Hospital. At the same time, the annual average of the incidence of diphtheria in the population of Aberdeen was 3·4 per 1000 of the population. The average daily number of diphtheria patients in the City Hospital during the ten years 1915–1924 was 31. From 1922 to 1925, however, the case-incidence of diphtheria in the City has been 1·9 per 1000 of the population, and the average daily number of diphtheria patients in hospital during these years has been 31. The figures are represented in Chart No. 2.



NOTE—Active immunisation against Diphtheria was commenced in January, 1922. The total number of individuals (nurses and maids) on the staff of the City Hospital may be put at 125.

It has to be noted that, prior to the institution of active immunisation in 1922, an average of 11 per cent. of the staff suffered annually from diphtheria, and since 1922, an average of 1·6 per cent. The diphtheria incidence in the

staff has been reduced from 18·4 per cent. in 1921 to 0–3·2 per cent. in the years 1922–1925.

Active Immunisation against Diphtheria of Patients admitted to Hospital with Scarlet Fever. Being convinced of the value of active immunisation against diphtheria in the City Hospital staff, occasion was taken a year ago to make this active protection against diphtheria available to scarlet fever patients admitted to hospital. Immediately on admission, scarlet fever patients are Schick-tested, and as soon as defervescence has occurred the positive reactors receive a first series of three immunising injections. These cases are being watched—they represent merely a trifling contribution to the numbers of Schick-positive reactors which are being immunised under the intensive immunising campaign which the Town Council have sanctioned.

Active Immunisation of School Children against Diphtheria. Children under seven years of age were eliminated from this group as they were suitable for immunising with the combined diphtheria and scarlatina prophylactic (see p. 347). In all, 734 school children have, to the end of September, 1926, received a first series of immunising injections of the diphtheria prophylactic. Of these 734 children, 201 were re-tested at the end of six months, and of these, 164, or 81·6 per cent., were found to be protected, as indicated by a negative Schick reaction. None of these 164 protected children has contracted diphtheria, although three of the children who had received a first series of injections and who had not yet been re-tested, developed diphtheria within five months of receiving the injections.

VI. CONCURRENT ACTIVE IMMUNISATION AGAINST DIPHTHERIA AND SCARLET FEVER.

Diphtheria Toxoid-Antitoxin and Scarlatinal Streptococcus Toxin. Combined Prophylactic.

Combined Diphtheria and Scarlatina Prophylactic. In initiating the campaign for the active immunisation of the population against diphtheria and scarlet fever, it was early apparent that there would be great practical difficulty in the way of securing active immunisation of the population of Aberdeen against diphtheria and scarlet fever unless such immunity could be secured at one and the same time by a combined inoculation. Not only so, but it was evident that if a community campaign for protection against diphtheria by means of diphtheria toxoid-antitoxin was initiated, and later it was found expedient to undertake a second community campaign for protection against scarlet fever, the response to the second campaign might be poor.

Experiments to determine Potency, Stability, and Safety of the Combined Diphtheria and Scarlatina Prophylactic. The following experiments were undertaken with a view to testing whether the two prophylactics could be combined with safety and with a satisfactory immunisation response:

1. *Toxicity Test on Animals.*

Diphtheria toxoid-antitoxin (B. W. and Co.) when injected into guinea-pigs is non-toxic in doses of 5 c.c.

To 5 c.c. quantities of diphtheria toxoid-antitoxin, 1 c.c. of *Streptococcus scarlatinae* toxin (15,000 skin doses) was added, and after allowing the mixture to stand for 24 hours at room temperature, this amount was inoculated into a series of guinea-pigs. No ill effects were observed.

Further tests were carried out with the same quantities after having been in admixture for two weeks, and again the response was found to be non-toxic.

These experiments served to demonstrate that no dissociation of the diphtheria toxoid-antitoxin and streptococcus toxin resulted in the production of a toxic product.

2. *Test of Animal Immunisation Response, by O'Brien.*

Dr O'Brien of the Wellcome Research Laboratories prepared a mixture of diphtheria toxoid-antitoxin and streptococcal toxin, and found that, when a series of guinea-pigs was inoculated with the mixture and another series was inoculated with diphtheria toxoid-antitoxin alone, the immunising power of the mixture (as estimated by the method of Glenny, Allen and Hopkins, 1923), was only slightly less than the immunising power of the toxoid-antitoxin given alone. The response to the streptococcus toxin cannot, of course, be measured on laboratory animals.

3. *Amount of Streptococcus Toxin used in Mixtures.*

Depending on the strength of the streptococcus toxin as judged by various Dick tests, so the actual quantity of streptococcus exotoxin added to the diphtheria toxoid-antitoxin is modified. If, for instance, the streptococcus toxin contains 15,000 skin doses per c.c., then to 25 c.c. quantities of diphtheria toxoid-antitoxin there is added 0·8, 1·6 and 4·8 c.c. of streptococcus toxin; representing approximately mixtures containing 500, 1000 and 3000 skin doses per c.c.

If 1 c.c. of the third mixture is injected, the addition of streptococcus toxin means a reduction of the dose of diphtheria toxoid-antitoxin to 0·8 c.c. instead of 1 c.c. as usually recommended.

4. *Application to Man.*

The experimental work on laboratory animals with the combined prophylactic, carried out as above indicated, appeared to demonstrate that the combined prophylactic could be used with safety and with a satisfactory immunising response in laboratory animals, and warranted its application to man. Preliminary experiments in testing out the combined diphtheria and scarlatina prophylactic on man were initiated in June, 1925—medical students and nurses being obtained as volunteers for the tests. It was rapidly ascertained that the local reactions from the combined injection were not of a severe nature, and that general disturbance and transient erythema occurred so rarely as to be negligible. In fact, the reactions obtained by the combined prophylactic have not been more serious than the reactions obtained by the scarlatinal streptococcus toxin alone.

In the first series of experiments half a dozen volunteer medical students and nurses, who had been found to be both Schick-positive and Dick-positive reactors, received concurrently as their first immunising injections 500 skin doses of streptococcus toxin into one arm, and 1 c.c. of diphtheria toxoid-antitoxin into the other arm. The reactions from these first injections being negligible, these volunteers received, a week later, an injection of the combined prophylactic containing 500 skin doses of streptococcus toxin and 1 c.c. of diphtheria toxoid-antitoxin; a week later they received a second injection of the combined prophylactic containing 1000 skin doses of streptococcus toxin and 1 c.c. of diphtheria toxoid-antitoxin; and a week later they received a third injection of the combined prophylactic containing 3000 skin doses of streptococcus toxin and 1 c.c. of diphtheria toxoid-antitoxin. Three months later all the six volunteers were found to be Dick-negative and

Schick-negative. These experiments were repeated on other volunteers, and the results as described above were confirmed. Further confirmation of these results was obtained by fully testing out the combined prophylactic on children under six years of age admitted to the tuberculosis and marasmus wards of the City Hospital. We were thus in a position to conclude that the combined prophylactic could apparently be used with as much safety as could the diphtheria prophylactic and scarlatina prophylactic when used separately.

Active Immunisation against Diphtheria and Scarlet Fever with Combined Prophylactic at Child Welfare Centres. An abundance of experimental data goes to show that from 80 to 90 per cent. of children under six years of age are susceptible to both diphtheria and scarlet fever, as shown by positive Schick and Dick tests, and, accordingly, no preliminary Schick-testing or Dick-testing is required in children in this age-period, and the actively immunising injections can be straightway administered. This elimination of the preliminary Schick and Dick tests in young children is of great practical importance. Thus, in immunising such children separately against diphtheria and scarlet fever, it was found that a single series of injections of streptococcus toxin and diphtheria toxoid-antitoxin respectively result in from 70 to 80 per cent. of the inoculated children in this, the most susceptible age-period, being protected. It is a matter of great practical moment in the immunising campaign that an assurance can be given to mothers that, by means of a single series of three injections of the combined prophylactic, some 75 per cent. of the children will be protected against both diphtheria and scarlet fever. Some experience is required in performing the Schick and Dick tests and in reading the results, and by eliminating the preliminary susceptibility tests, private medical practitioners, by administering the immunising injections, can co-operate in the community campaign to the greatest extent, while the preliminary tests in adults and older children and the re-testing of the children who have received their first series of immunising injections can be undertaken by the medical staff of the Health Department.

Another consideration of great practical importance is to the effect that children under seven years of age tolerate the injections extremely well. Adults and older children are much more sensitive to the injection of foreign proteins, and this fact emphasises the desirability of the immunising injections being provided as soon as children are aged one year, and when, thereafter, the protection accorded will be available during the more susceptible years of the child's life. It is to be noted in passing that the immunity to scarlet fever and diphtheria, as indicated by negative Dick and Schick reactions in children during the first year of life, is apparently passive in character, and is assumed to be obtained *in utero* from the mother's blood and from the mother's milk during lactation, and quickly decays. We have adopted the age-period of one year as the optimum period for the immunisation of children against diphtheria and scarlet fever after due deliberation. The susceptibility tests would indicate that the six months age-period rather than the one year age-period is the optimum, but at six months the normal child is teething, and at this age-period the pancreas is assuming its adult

function. At the nine months age-period, the normal child is possibly in process of weaning, and, accordingly, it has seemed best to defer the offer of immunisation against diphtheria and scarlet fever until the age-period of one year, at which age-period susceptibility to diphtheria and scarlet fever is still increasing.

Experimental data and hospital experience having indicated the safety and competency of the combined prophylactic, a beginning was made with the immunising of children over one year at the Child Welfare Centres in November, 1925, and, up to the end of September, 1926, 524 children have received a first series of immunising injections of the combined prophylactic. This experience of the immunising of the infant population, limited as it is, has impressed us with the urgency of the need for securing an immunising mixture that will provide protection against scarlet fever and diphtheria with the fewest possible number of injections. Even when the preliminary susceptibility tests are eliminated, it is found in practice that mothers are altogether reluctant to have their children re-tested after the first series of immunising injections, and for this reason, and in order to encourage the widest number of parents to secure this immunising device for their children, it is proposed to delay the re-testing of these children until they enter school at the five year age-period.

Active Immunisation against Diphtheria and Scarlet Fever with Combined Prophylactic in School Children. School children are more sensitive to the injection of the combined prophylactic than are children in the 0–5 year age-period, and in school children over seven years of age, preliminary Schick and Dick testings are accordingly indicated. Susceptibility to one or other or to both diseases having thus been ascertained, the immunisation indicated can then be produced. The sanction of the Aberdeen Education Authority having been obtained to the comprehensive immunisation of school children in November, 1925, we accepted responsibility for the immunising procedure in the schools. A total of 1305 school children who were found to be Dick-positive and Schick-positive reactors received a first series of immunising injections of the combined diphtheria and scarlatina prophylactic. Of these 1305 children, 151 were re-tested at the end of three months, with the following result: 121 of the 151 children, or 80 per cent., were found to be Dick-negative; 16, or 11 per cent., were found to be mildly Dick-positive; and 14, or 9 per cent., were markedly Dick-positive. Some 82, or 54 per cent., were found to be Schick-negative; 38, or 25 per cent., were found to be mildly Schick-positive; and 31, or 21 per cent., markedly Schick-positive. Again it has to be noted that statistical data of any value will not be available in connection with the effect of this immunising procedure in preventing the incidence of diphtheria and scarlet fever in school children for several years. Six of the 1305 children who had received a first series of immunising injections of the combined prophylactic and who had not been re-tested developed scarlet fever—1, two months later; 2, four months later; 2, six months later; 1, eleven

months later. Two developed diphtheria—1, three months later; 1, eleven months later.

VII. PASSIVE IMMUNISATION AGAINST SCARLET FEVER.

Passive Immunisation of Scarlet Fever Contacts. The ideal procedure with scarlet fever contacts would be immediately to immunise passively all positive reactors by means of an injection of scarlatinal antistreptococcus serum, and to proceed a month later to produce an active immunity with streptococcus toxin. The increase in the number of injections, and the length of time over which such injections have to be made, make contacts reluctant to secure such comprehensive protection.

Having in view the mild type of scarlet fever that at present prevails, the practice in Aberdeen is to allow contacts to take their chance of an immediate infection, and to urge the desirability of securing an enduring active protection. This applies to the limited number of contacts that occur in any private house. In the event of an outbreak of scarlet fever in an institution, however, or in the event of the cross-infection of a diphtheria ward with scarlet fever, the withholding of a passively immunising injection from the contacts who are positive reactors could not be justified. On the contrary, under such circumstances scarlatinal antistreptococcus serum as a passively immunising agent provides a certain method of controlling the infection.

The following experience indicates the advantage that follows from knowing the susceptibility of contacts to scarlet fever as indicated by the readings of the Dick reactions, and the necessity for accurately determining the prophylactic dose of antitoxic serum. Table XI shows how, in the Royal Hospital

Table XI.

Initials	Age	Sex	Dick test +	Dick test −	Scarlet fever antitoxin	Dick re-test +	Dick re-test −
A. H.	8/12	M.	+	Nil	2·5 c.c. serum No. 1 (concentrated)	Nil	−
M. A.	9/12	F.	+	,,	2·5 ,, ,, ,,	,,	−
C. W.	4	M.	+	,,	5 ,, ,, ,,	,,	−
M. D.	4	F.	+	,,	5 ,, ,, ,,	,,	−
W. D.	8	M.	+	,,	5 ,, ,, ,,	,,	−
A. S.	8½	M.	+	,,	5 ,, ,, ,,	,,	−
C. G.	4	M.	+	,,	5 ,, ,, ,,	,,	−
I. D.	1¼	F.	+	,,	5 ,, ,, ,,	,,	−
A. D.	3½	M.	+	,,	10 c.c. serum No. 2 (non-concentrated)	,,	−
D. F.	1½	M.	+	,,	10 ,, ,, ,,	,,	−
D. P.	6½	M.	+	,,	10 ,, ,, ,,	,,	−
E. S.	1¾	F.	+	,,	10 c.c. serum No. 3 (non-concentrated)	,,	−
M. W.	2½	F.	+	,,	10 ,, ,, ,,	,,	−
G. L.	2¾	M.	+	,,	10 ,, ,, ,,	,,	−
A. C.	2¾	M.	+	,,	15 ,, ,, ,,	,,	−

for Sick Children, from the surgical wards of which a case of clinical scarlet fever had been removed, passive immunity was efficiently secured by first Dick-testing all the contacts and passively immunising the positive reactors with 2·5 c.c. or more of concentrated and non-concentrated antistreptococcic

serums. None of the children had previously had scarlet fever. (This also applies to Tables XII and XIII.)

None of the contacts recorded in Table XI contracted scarlet fever, and on re-testing 24 hours after administration, the efficacy of these serums was indicated by the fact that all these Dick-positive reactors had become Dick-negative.

As contrasted with this result, Table XII refers to an experience in the same hospital, in the medical wards of which there had also developed a case

Table XII.

Initials	Age	Sex	Dick test +	Dick test −	Scarlet fever antitoxin	Dick re-test +	Dick re-test −
*L. R.	10	F.	+	Nil	10 c.c. serum No. 4 (non-concentrated)	+	Nil
*G. H.	1	F.	+	,,	20 ,, ,, ,,	+	,,
A. S.	12	F.	+	,,	10 ,, ,, ,,	+	,,
J. P.	9	M.	+	,,	10 ,, ,, ,,	+	,,

Two of these (*) contracted scarlet fever after the injection of this non-concentrated serum.

of scarlet fever. In this case, the Dick-positive contacts each received 10 c.c. or more of a non-concentrated antistreptococcic serum (No. 4), and the table shows that even 20 c.c. of this serum failed to convert the Dick-positive reactors to Dick-negative reactors, and the absence of protective antibodies was indicated by the fact that two of the contacts developed scarlet fever.

Similarly, scarlet fever developed in the reception ward at the City Hospital, and seven susceptible contacts, Dick-positive reactors, were immunised with non-concentrated antistreptococcic serum (No. 5). Reference to Table XIII shows that the dose of serum given to seven children varied from 10 c.c. to 30 c.c. Nevertheless, a brother and sister who received intramuscularly 10 c.c. of serum both developed scarlet fever three days later.

Table XIII.

Initials	Age	Sex	Dick test +	Dick test −	Scarlet fever antitoxin	Dick re-test +	Dick re-test −
M. M.	6	F.	+	Nil	15 c.c. serum No. 5 (non-concentrated)	+	Nil
J. T.	8	M.	+	,,	20 ,, ,, ,,	+	,,
G. I.	4	M.	+	,,	25 ,, ,, ,,	+	,,
A. F.	9	F.	+	,,	30 ,, ,, ,,	+	,,
M. W.	12	F.	+	,,	20 ,, ,, ,,	+	,,
*M. M.	8	F.	+	,,	10 ,, ,, ,,	+	,,
*J. M.	5	M.	+	,,	10 ,, ,, ,,	+	,,

Two of these (*) contracted scarlet fever after the injection of this non-concentrated serum.

It might be argued that these prophylactic measures failed because the brother and sister who had received 10 c.c. of serum were already in the prodromal period, but further experience has indicated that a potent serum may cut short the disease, not only in the period of incubation, but during the period of onset.

These isolated results are submitted as examples of the efficacy of a potent scarlatinal antistreptococcus serum as an efficient prophylactic when given in

sufficient amount, and experience has shown that 5 c.c. of certain concentrated scarlatinal antistreptococcic sera are an efficient prophylactic. It only remains to be said that, with the serum therapy and prevention of scarlet fever in its present experimental position, it would be unfair to publish results contrasting one serum with another, but the experience has been frequently repeated in the City Hospital wards, since the above results were recorded, that the administration of 5 c.c. of a concentrated antistreptococcic serum containing 2500 antitoxin units to susceptible contacts entirely prevents the spread of the disease. From the administrative point of view, it will be readily recognised that it is extremely awkward to give a serum for purposes of passive protection and to find that the serum fails to do its work.

VIII. SERUM TREATMENT OF SCARLET FEVER.

A preliminary analysis of the results of 500 cases of mildly or moderately ill cases of scarlet fever (excluding profoundly toxic and septic cases) treated with serum in the City Hospital, as contrasted with an analysis of the results of 500 cases of scarlet fever which did not receive serum, is set forth in Table XIV.

Table XIV. *Analysis of* 500 *Control Cases and* 500 *treated with a Concentrated Antitoxic Antibacterial Serum.*

	Control without serum	Control with concentrated serum
No. of cases	500	500
Amount of serum	—	12·2 c.c.
Days in hospital	36·7	28
Return cases	21·8 %	10 %
Acute Otitis	10·8 ,,	3·7 ,,
Acute Mastoiditis	1·1 ,,	—
Adenitis	15·4 ,,	3·7 ,,
Arthritis	3·0 ,,	0·8 ,,
Nephritis	2·8 ,,	0·2 ,,
Rhinorrhoea	0·4 ,,	1·4 ,,
Serum disease	—	23·7 ,,
Deaths	1·1 ,,	—

It would appear from Table XIV that serum treatment, particularly with a potent serum, is capable of reducing the average stay of scarlet fever patients in hospital, and of reducing the serious complications of the disease and the number of return cases. The reason for excluding the grave toxic and septic cases of scarlet fever from this preliminary comparison of serum treated cases of scarlet fever with cases that did not receive serum, is dependent on the fact that during the present epidemic prevalence of scarlet fever the disease has been of a milder description than was the case during the years 1923–1924, from which the statistics of control cases (not receiving the serum treatment) are taken. It will be obvious that for purposes of a proper comparison the figures should have related to the same period, and every alternate case only should have received serum; but the efficacy of the serum in causing defervescence and subsidence of symptoms within 24 hours was so apparent in the

early stages of the application of serum therapy that it appeared that it would not be legitimate to withhold serum treatment to the extent that such an arrangement would have implied.

Treatment of Toxic and Septic Cases of Scarlet Fever.

Recent work on the etiology of scarlet fever would indicate that in both toxic and septic cases of scarlet fever the *S. scarlatinae* is the causative organism; that in toxic scarlet fever the scarlet streptococci produce toxins that are immediately absorbed and produce an overwhelming poisoning of the whole body and that in septic scarlet fever the streptococci and their toxins produce their main damage in various local foci.

Treatment of Toxic Cases of Scarlet Fever. Apart from the experience of the serum treatment of some 500 cases of mild or moderately ill scarlet fever as above recorded, Taylor has had experience, from September, 1925, of the treatment of eight cases of toxic scarlet fever in all. His results with these eight toxic cases have been as remarkable as, or even more remarkable than those obtained in treating ordinary cases. It is as essential, however, to give large doses of scarlatinal antistreptococcic serum in toxic cases as it is to give large doses of diphtheria antitoxin in toxic cases of diphtheria. Thus it has been found that, within 12 hours of the intravenous administration of from 50 to 100 c.c. of the concentrated antistreptococcus serum, the signs and symptoms of profound toxaemia have disappeared, consciousness is regained, the cardiac condition is much more satisfactory, the temperature falls practically to normal, and meningeal symptoms which are frequently present in such cases largely subside. In short, the prognosis in toxic cases of scarlet fever changes in the majority of cases from grave to hopeful after serum treatment.

Treatment of Septic Cases of Scarlet Fever. Taylor's experience has been limited to twelve cases, but, in these, much benefit was derived from this specific therapy, provided the serum was given in large amounts within 48 hours of the onset of the illness. This limited experience, however, indicates that, if serum treatment is not applied until after the first two days of illness, the septic complications of the disease appear to manifest themselves independent of the amount of serum administered. In other words, once what are known clinically as the septic complications of scarlet fever have manifested themselves, serum therapy has but little or no effect upon their progress.

Limited as our experience has been of the value of antitoxic serum in the treatment of scarlet fever, we are nevertheless satisfied that further experience will entirely justify our view that in scarlatinal antistreptococcus serum there has been made available for scarlet fever a specific therapy of the highest order.

IX. SUMMARY.

1. Scarlatinal streptococci obtained from the throats of cases of scarlet fever can be divided into various groups by means of agglutination and absorption tests. The same type of streptococcus can on occasion originate at least five separate clinically distinguishable diseases, namely, scarlet fever, tonsilitis, erysipelas, puerperal fever, and broncho-pneumonia, and it would appear that, so far as streptococcic infections are concerned, the nature of the disease entity is determined by the toxigenic qualities of the type of streptococcus, by the susceptibility or insusceptibility of the individual as determined by the absence or presence of the specific antibodies in the blood, and by the site of the infection itself (see p. 330).

2. Strong corroboration for the view that the *S. scarlatinae* is the causal organism of scarlet fever is obtained from the following findings, viz.:

(*a*) *S. scarlatinae* have been isolated from the throat brushings of practically all acutely ill scarlet fever patients (see p. 329).

(*b*) The whole clinical picture of scarlet fever going on to marked desquamation is produced by the subcutaneous injection of the exotoxin derived from the *S. scarlatinae*, the exotoxin having been heated to 55° C. for one hour, with a view to destroying any filterable living virus which might be associated with the filtered exotoxin (see p. 342).

(*c*) In the Schultz-Charlton reaction the blanching of the scarlet fever rash is caused by the serum of a horse immunised against *S. scarlatinae* and its toxins.

(*d*) Dick-positive and Dick-negative reactions as produced by the intradermal injection of the streptococcus toxin have the closest correspondence to the degree of susceptibility or immunity to scarlet fever of the respective reactors (see p. 334).

(*e*) Susceptible nurses once they are actively immunised by injections of scarlatinal streptococcus toxin have been shown to be immune to the toxin of scarlet fever (see p. 337), and susceptible school children similarly inoculated are likewise immune (see p. 338).

(*f*) Return cases of scarlet fever can be prevented by actively immunising susceptible contacts with scarlatinal streptococcus toxin prior to the scarlet fever patient being discharged from hospital (see p. 339).

(*g*) Susceptible contacts can be safeguarded from taking scarlet fever by passively immunising them with a sufficient dose of antistreptococcus serum obtained from a horse which has been immunised by injections of *S. scarlatinae* and its toxin (see p. 349).

3. The limitations of the Schultz-Charlton reaction as an aid in the diagnosis of scarlet fever have been confirmed (see p. 330).

4. Evidence has been obtained which firmly establishes the value of the Dick susceptibility test as a measure of susceptibility to scarlet fever (see p. 332).

5. Extensive corroboration of the value of the Schick test as a measure of susceptibility to diphtheria has been obtained (see p. 334).

6. The efficacy of active immunisation against scarlet fever by means of scarlatinal streptococcus toxin injections has been demonstrated by the fact that, while scarlet fever has been present in epidemic form in Aberdeen, no nurses or maids in Aberdeen City Hospital have contracted scarlet fever since June 1st, 1925, from which date the nursing and domestic staffs of the hospital have been actively immunised before being admitted for duty to the scarlet fever wards; whereas, prior to that date, an average of 8·5 nurses, or 9·5 per cent. of the nursing staff, and 1·4 maids, or 4·2 per cent. of the domestic staff, annually suffered from scarlet fever (see p. 337).

7. Coincident with the disappearance of scarlet fever in the immunised nursing staff of the City Hospital, there has been a notable increase in the incidence of streptococcic tonsilitis in these immunised nurses, and the streptococci obtained from these cases of tonsilitis in nurses commonly fall into one or other of the serological groups of scarlatinal streptococci; and accordingly it would appear to be proved that immunised nurses, while protected by immunisation from the toxic effects of the exotoxin of *S. scarlatinae*, are not protected against tonsilitis due to *S. scarlatinae* (see p. 338).

8. It has been demonstrated that return cases of scarlet fever can be prevented by Dick-testing all the inmates of the house from which a scarlet fever patient has been removed to hospital and thereafter immunising the Dick-positive reactors—the three injections of streptococcus toxin in 500, 1000, and 3000 skin doses respectively being given at intervals of 5 days, and resulting in an active immunity as judged by a negative Dick reaction being developed 14 days after the third injection (that is, 24 days after the case of scarlet fever has been removed to hospital). Accordingly, when the scarlet fever patient is discharged from hospital, he returns home to a family, the susceptible members of which have all been immunised against scarlet fever (see p. 339).

9. The finding that immunity to scarlet fever develops 14 days after the third immunising injection has been corroborated, and accordingly reason is given for the belief that this actively immunising device will prove of great value in the early control of scarlet fever during its epidemic prevalence (see p. 340).

10. The urgency of the need for the provision of a detoxified scarlatinal streptococcus toxin or toxoid has been indicated, and a potent non-irritant streptococcus anatoxin has been prepared, which it is believed will profoundly facilitate the immunising campaign against scarlet fever (see p. 342).

11. The efficacy of active immunisation against diphtheria by means of diphtheria toxoid-antitoxin injections has been demonstrated by the fact that since January 1st, 1922, the incidence of diphtheria in nurses and maids in Aberdeen City Hospital has been reduced from an annual average of

11 per cent. of the staff prior to 1922 to an average of 1·6 per cent. during the years 1922–1925 (see p. 344).

12. It has been demonstrated that diphtheria toxoid-antitoxin can be used in admixture with scarlatinal streptococcus toxin as a combined diphtheria and scarlatina prophylactic. The experiments have proved that the combined prophylactic can be used with as much safety as can the diphtheria prophylactic and scarlatina prophylactic used separately. In testing out the immunising action of the combined prophylactic in about 2000 children, it has been shown that the immunisation response is of a high order (see p. 348).

13. It has been demonstrated that 5 c.c. of a potent scarlatinal antistreptococcic serum, containing 500 antitoxin units per c.c., invariably produces a satisfactory passive immunity in susceptible scarlet fever contacts and prevents them contracting the disease. In view of the fact that an active immunity to scarlet fever can be induced within 24 days, it has not been considered necessary to make this passively immunising device available for scarlet fever contacts in private houses as a routine, such contacts being allowed to take their chance of an immediate infection and being urged to secure an enduring active immunity. In the event of an outbreak of scarlet fever in an institution, however, or in the event of the cross-infection of a diphtheria ward with scarlet fever, the withholding of a passively immunising injection from the contacts who are positive reactors cannot be justified. On the contrary, the evidence submitted goes to prove that, if the dose of antistreptococcus serum is sufficient, then the passive immunity induced by it is a certain method of controlling the infection (see p. 349).

14. Evidence is submitted which goes to show that a potent antistreptococcus serum, 1 c.c. of which contains 500 streptococcus antitoxin units, is a specific therapy for scarlet fever of a high order. Suitable doses of the antistreptococcus serum vary from 10 c.c. to 100 c.c. according to the toxicity of the case. The serum has an immediate effect in reducing temperature and alleviating other symptoms, and is capable of reducing the serious complications of the disease, the number of return cases, and the average stay of scarlet fever patients in hospital. The benefit derived by toxic and septic cases of scarlet fever is even more evident. Admirable results are obtained in all cases if the serum is administered within 48 hours of the onset of illness. Once septic complications of scarlet fever have manifested themselves, serum therapy has but little or no effect in determining their progress (see p. 351).

X. CONCLUSION.

From the evidence submitted it appears reasonable to conclude that the comprehensive control of the incidence of scarlet fever and diphtheria in the community will be obtained when the newer methods of immunising against these diseases have been generally adopted.

REFERENCES.

Dick and Dick (1923). *J. Amer. Med. Assoc.* **81**, 1166.
—— (1924). *Ibid.* **82**, 265.
Dochez (1925). *Medicine*, **4**, 251.
Gabritschewsky and Langowoi (1907). *Berl. klin. Wochenschr.* **44**, 556.
Glenny, Allen and Hopkins (1923). *J. Exper. Path.* **4**, 19.
Glenny (1925). *J. of Hygiene*, **25**, 90.
Larson, Evans and Nelson (1924). *Proc. Soc. Exp. Biol. and Med.* **22**, 194.
Larson and Eder (1926). *J. Amer. Med. Assoc.* **86**, 998.
Loeffler (1884). *Arb. a. d. K. Gesundh.* **2**, 421.
Marmorek (1895). *Ann. Inst. Pasteur*, **9**, 592.
Moser (1902). *Wien. klin. Wochenschr.* **15**, 1053.
Park (1913). *Amer. J. Obst.* **68**, 1213.
—— (1915). *Ibid.* **71**, 363.
—— (1918). *Trans. Assoc. Amer. Physicians*, **33**, 55.
Polotevkova (1921). *Russk. Wratch.* **11**, 1183.
Savchenko (1905). *Ibid.* **4**, 797.
Schick (1908). *München. med. Wochenschr.* **55**, 504.
Schultz and Charlton (1918). *Zeitschr. f. Kinderh.* **17**, 328.
Smith, J. (1926). *J. of Hygiene*, **25**, 165.
Smith, J. and Taylor (1926). *Ibid.* **25**, 90.
Smith, Th. (1907). *J. Exper. Med.* **2**, 241.
Zingher (1915). *Amer. J. Obst.* **72**, 735.
—— (1915). *Amer. J. Obst. Med. Rec.* **87**, 752.
—— (1916). *Amer. J. Dis. Child.* **11**, 269.

(*MS. received for publication* 16. iv. 1927.—Ed.)