AN EPIDEMIOLOGICAL STUDY OF DIPHTHERIA IN A REMOTE NEW ZEALAND COMMUNITY.

By C. E. HERCUS, R. A. SHORE, H. E. BARRETT and J. H. NORTH.

(*From the Department of Public Health, Otago University.*)

(With 1 Figure.)

CONTENTS.

1. Introduction.

In the practical instruction of Preventive Medicine which is given in the University of Otago, during the fifth of the six years comprising the medical course, each student carries out an investigation into some subject relating to the prevention of disease. The present study was carried out by two students (J. H. N. and H. E. B.). Since certain amplification was necessary, it was thought advisable that the Medical Officer of Health (R.A.S.), and the Professor of Public Health (C. E. H.), should associate themselves with the presentation of this investigation.

The study deals with two outbreaks of diphtheria which occurred during 1926 in the isolated coal-mining "township" of Kaitangata in the South Island of New Zealand. This community is situated on the banks of the Clutha river 52 miles south of Dunedin, the capital of Otago province. The population in 1926 numbered 1750. The houses are well built and roomy and number 4·4 to the acre. The climate is very similar to that of England. The standard of living, and the general and personal hygiene, is distinctly high.

For over six years prior to 1926 there had been a noteworthy absence of epidemic disease. No cases of diphtheria were notified between 1920 and 1923. In 1924 there were 7 cases, of which 5 came from one family. In 1925, 3 cases were reported, each from a separate household.

2. The Distribution and incidence of diphtheria in 1926.

Between March 8th and November 17th, 1926, 104 cases of diphtheria were notified from Kaitangata. The morbidity was therefore 59·4 per 1000 compared with 1·5 per annum for the whole dominion of New Zealand during 1926.

The average incidence for diphtheria in London, for the decennium 1917–1926, was 1·7 per 1000 per annum. Therefore the amount of diphtheria morbidity which was caused by this epidemic in rural New Zealand was equivalent to about 30 years of the London endemic.

Fig. 1 gives an incidence histogram of the 104 diphtheria patients. If 8 sporadic cases, which were notified between May and September are excluded,

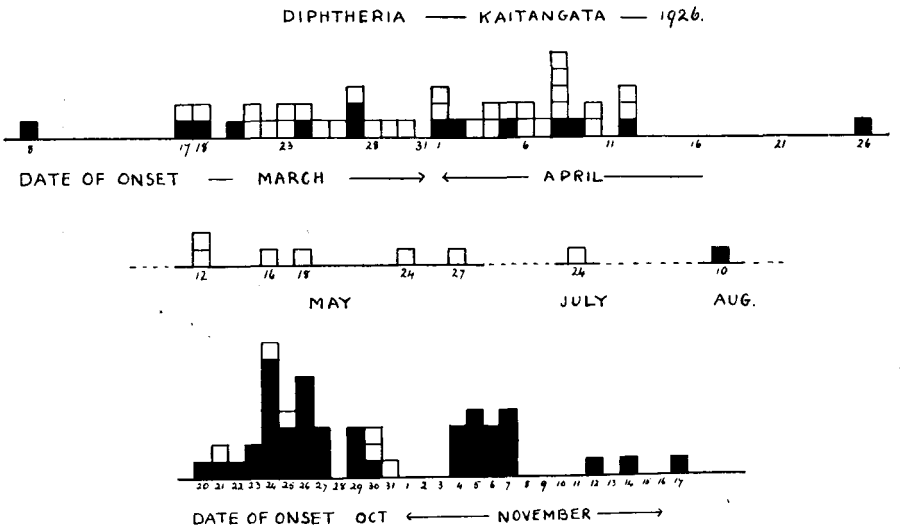

Fig. 1. Each square ≡ to a case of diphtheria, the black squares represent those persons who received milk from one suspected vendor.

the remaining patients fall into two groups: one in March and April comprising 45, another in October and November with 51 diphtheria patients. Owing to the reversal of the seasons in the southern hemisphere, the March-April outbreak was in the autumn, and the October-November prevalence was in the spring.

Examination of Fig. 1 shows that although there was no significant difference in the total duration of the two outbreaks, if the first and last of the autumn cases are ignored, yet the October-November cases were further concentrated into two main groups or "explosions" of infection. Moreover, there was a distinctly greater tendency for multiple infections to originate on the same day in October and November than in March and April. This is indicated by the fact that 3 or more cases were notified on one day on ten occasions, in October and May, as against 4 in the autumn. There was, however, no significant difference between the spring and autumn outbreak in the occurrence of multiple infections in one household. Thirty-four houses produced 45 cases

in March and April, while in the following spring the 51 patients came from 37 households. The latter cases were, as a group, more severe clinically than the former.

3. AGE DISTRIBUTION.

The school age in New Zealand is from 5 to 15. Table I therefore gives the distribution of the diphtheria cases among the pre-school, school and post-school divisions of the population. The figures, though small, show a distinct concentration of attack on the school-age group, which was much more marked in March and April than during the spring. In the autumn three-quarters of the cases were among the school children, whereas, in October and November, infected infants and adults together outnumbered the diphtheria cases among those children who were attending school. The last column in Table I gives

Table I. *Diphtheria. Kaitangata*, 1926.

		Cases of clinical diphtheria						
		March and April		Oct. and Nov.		Total		London % distribution of cases
Age group	No. in group	No.	% cases	No.	% cases	No.	% cases	
0–5	200	3	*7*	12	*24*	15	*16*	*25*
5–15	380	33	*73*	23	*45*	56	*58*	*49*
15+	1170	9	*20*	16	*31*	25	*26*	*26*
Totals	1750	45	*100*	51	*100*	96	*100*	*100*

The table shows the greater concentration of the infection on the school-age group (5–15) in the first outbreak, and the relatively greater incidence among infants and adults during the following spring (October and November).

the percentage distribution of cases among the three similar age groups in London. It is seen that the distribution in October and November is remarkably similar in London and rural New Zealand, but in the autumn relative number of infections of the 5–15 group was much higher in New Zealand than London, which hints that in an unsalted community a day school becomes relatively a more important centre of dissemination of infection than in cities where diphtheria has been endemic for many years. Table I indicates that the school was the chief centre of dissemination of infection, especially in the first outbreak—a deduction which is further confirmed by analysis of the incidence of infection in the school itself.

The school children are divided into seven educational standards which occupy six separate class rooms. Table II gives the incidence of diphtheria in these standards, and also the floor area per head as an index of the degree of crowding. In the first outbreak the morbidity was significantly higher in Standards I and III than among the occupants of the other rooms. The lowest standard, usually the most susceptible group in town schools, escaped lightly in the autumn, only to produce the highest attack rate in the spring. The table suggests that infection spread most easily in two school rooms in the first outbreak, whereas in the second outbreak, there is only a slight indication that one room was more dangerous than the others. The mode of onset of the two outbreaks also presents a contrast. In April the first 4 cases were all

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Table II. *The incidence of diphtheria in Kaitangata school giving the distribution in class rooms.*

School standard class rooms	Number of occupants	Sq. feet of floor space per occupant	Diphtheria morbidity: March–April Observed numbers	March–April Expected numbers	Oct.–Nov. Observed numbers	Oct.–Nov. Expected numbers	Total Observed numbers	Total Expected numbers
Primary	126	18	4	11·0	13	7·7	17	18·6
I	60	14	13	5·2	2	3·7	15	8·9
II	49	15	1	4·3	3	3·0	4	7·2
III	49	13	9	4·3	2	3·0	11	7·2
IV	38	14	3	3·3	1	2·3	4	5·6
V and VI	58	10	3	5·1	2	3·5	5	8·6
Totals	380	av. 14	33	33·2	23	23·2	56	56·1
		χ^2	24·6453		6·1682		9·7327	
		ρ	0·0002		0·2918		0·0843	

During March and April the majority of infections came from two class rooms (Standards I and III) suggesting a special influence in these rooms (? carriers). When the ordinary "goodness of fit" test is applied the distribution of cases throughout the classes in March and April is very unlikely to have been a random one. In October and November, when the infection was, undoubtedly, mainly by milk, the distribution in the classes *may* be a random one, but the higher morbidity in the primary class might have partly been caused by class-room contact.

from Standard III; the next 4 cases in Standard I. Moreover, 2 of the cases in Standard III were house contacts of children in Standard I; demonstrating very nicely how the two school rooms were linked by the home contacts. It is noteworthy also that the 9th and 10th cases to be reported were the schoolmistress of Standard I and the janitress of the school respectively. Therefore in the first outbreak 2 of the only 9 adults who contracted diphtheria were school officials. In the October epidemic the first 3 cases came from three different school standards, and three separate houses, and therefore had no known contact with each other either in the school or the house. Lastly, Table II shows little tendency for diphtheria to attack junior more than senior children, such as is always seen in London schools. This suggests that the older children in Kaitangata were no more immune than the younger.

4. The relation of the milk supply to the distribution of cases.

The main contrasts between the October-November outbreak and that in autumn were, the more explosive nature of the former, the greater incidence among infants and adults than school children, the lack of any obvious contacts between the first victims of the outbreak, and the greater severity of the symptoms in October and November. These differences suggested an investigation of the milk supply. The community was served by two principal milkmen, who supplied 102 and 104 households respectively, 32 other families received milk from two smaller vendors, the remaining households had their own supply.

Table III gives the relation of diphtheria cases to the sources of supply. In the first outbreak there is no indication that the milk from one source was

more dangerous than another. But in the second outbreak no less than 46 out of 51 cases were supplied by the same milkman. In contrast, not one of the customers of milkman B., who had just as large a connection, contracted diphtheria in the October outbreak. Further, if the population is divided into those who received milk from the suspicious source and those who did not, the incidence during October and November in the former group was 30 times that in the latter. In the preceding autumn, it is true, the customers of milkman A. suffered the highest morbidity, but at this time the difference was

Table III. *Diphtheria incidence in relation to the milk supply.*

Milk supplied by vendor	Total households supplied	Infected with diphtheria: March and April, No. of cases	March and April, No. of houses	Oct. and Nov., No. of cases	Oct. and Nov., No. of houses	Population who used supply	Diphtheria morbidity %: March–April	Diphtheria morbidity %: Oct.–Nov.
A	102	15	10	46	34	370	4·1 ±1·0	12 ±1·1
B	104	11	9	0	0	1380	2·2	0·4
?	?	19	15	5	3			
Totals	?	45	34	51	37	1750	2·6 ±0·13	2·9 ±0·13

The distribution of cases in relation to the milk supply suggests that in the October-November outbreak, the milk sold by vendor A. was infected with diphtheria bacilli. The incidence among the users of this supply was 12 per cent., as against 2·9 for the whole population (including those who drank A.'s milk). The difference, 9·1, is eight times its probable error, 1·1.

The morbidity among the users of supply A. in March and April was also higher than the expected incidence as 4·1 is to 2·6, but since this difference, 1·5, is little larger than its probable error, 1·1, there is no statistical evidence that A.'s milk was responsible for the March-April outbreak, which, for other reasons, was considered to be air-borne.

hardly significant. Other evidence which incriminates milk as the main source of diphtheria infection in the spring outbreak is that one of the 8 sporadic cases, which were reported in the winter between the two main outbreaks, was a child in milkman A.'s family. On August 8th this child contracted laryngeal diphtheria which necessitated tracheotomy. On October 22nd a child of one of milkman A.'s dairymen contracted diphtheria. Finally the milkman himself, who gave a history of a sore throat for 6 weeks previously, was notified as a case of diphtheria on November 12th. Therefore it seems more than probable that this milk-vendor's farm was harbouring diphtheria bacilli during the whole period between August 8th and November 12th. Fig. 1 suggests that the milk was heavily infected on two occasions at least. The first being responsible for the October cases, the second causing the solid block of 14 cases, representing 11 households, which occurred between the 4th and 7th of November. Only two of the households, which were infected in the earlier part of the year, were reinfected in the spring epidemic. In one family, where two adults and a child had previously been infected, a third adult went sick. In the other house, a child who had had a severe attack in April, again contracted mild diphtheria in October. It is worth noting that it was not necessary for all milkman A.'s customers to receive infected milk, because the milk of the whole herd was not mixed before its distribution. The milk was strained and cooled in the same cans as it was taken round in; therefore only one can of several might be infected by one milker who was "carrying" diphtheria.

The milk was always delivered within 12 hours of milking. The limitation of the diphtheria cases almost entirely to one source of supply, a farm from which three cases of diphtheria had been recently notified, is strong evidence that the recurrence of diphtheria in Kaitangata was due to infection of this milk. The missing link in the evidence is the failure actually to isolate diphtheria bacilli from the suspected milk.

5. Schick testing and active immunisation in April.

Since 1921 it has been the custom, in the event of outbreaks of diphtheria occurring within reasonable distance of the Medical School in Dunedin, to Schick test all children whose parents consent to the procedure, to immunise the positive reactors with toxin-antitoxin mixture, and subsequently to test their immunological response by repeating the Schick reaction. Although the epidemic recorded above occurred at a distance of over 50 miles from Dunedin, conveniently accessible only by motor-car, it was decided in April to Schick test and actively immunise the children of Kaitangata in order to study the effects of isolation on their immunity. The October epidemic, which broke out immediately prior to the date fixed for the repetition of the Schick reaction, added considerable interest to the investigation.

The toxin used for the Schick reaction was the product of the Commonwealth of Australia's Serum Laboratories and was prepared from the toxic strain of *B. diphtheriae*, Park No. 8. This toxin had a titre of 35 M.L.D.'s per c.c. The toxin was diluted in the Dunedin laboratory at 7 a.m. on the morning of the test with normal saline of a *p*H of 7·8. The dilution was such that 0·2 c.c. contained $\frac{1}{50}$ of a guinea-pig M.L.D. The control consisted of the same dilution of toxin heated to 70° C. for five minutes. During transport to Kaitangata by motor-car, the diluted toxin was exposed to considerable shaking for a period of approximately 3 hours owing to the bad condition of the roads. The test was commenced at 10 a.m. on April 11th, three hours after diluting the toxin used in the Schick tests.

Table IV. *Schick reactions in Kaitangata school*, 1926.

	March and April			Oct. and Nov.						
		Schick negative			Schick negative			% Schick + in April		
Age Group	No. tested weak toxin	No.	%	Re-tested potent toxin	No.	%	Corrected % immune in April	As found	As estimated	Total diphtheria morbidity %
0–5	94	55	*58*	5	2	*40*	*23*	*42*	*77*	*7·5*
0–10	153	100	*65*	18	6	*33*	*22*	*35*	*78*	*19*
0–15	100	51	*51*	25	7	*28*	*14*	*49*	*86*	*11*
0–15	347	206	*59*	48	15	*31*	*18*	*51*	*82*	*12*
No. of column	1	2	3	4	5	6	7	8	9	10

The number of Schick negative reactors which were obtained by the use of a deteriorated toxin in April (col. 2) were too low. A retest in November of a sample of the April "immunes" demonstrated that the majority would have been Schick positive if a fully potent toxin had been used. Columns 7, 8 and 9 are obtained by correcting column 3 by column 6, on the assumption that the frequencies shown in column 6 were representative of the whole group (col. 2) and that no increase in Schick immunity had taken place in the interval between the original and repeated Schick tests.

The technique adopted was that of Zingher[1]. The results were read three days later, and were classified according to the standards laid down by the Medical Research Council[2]. Three hundred and forty-seven, out of approximately 600 of the population who were below 15 years of age, submitted to be Schick tested in April towards the close of the autumn outbreak. The results are shown in Table IV, col. 3. Only 40 per cent. of the children gave positive reactions. This was an unexpectedly low figure, because in a similar isolated rural community, Mosgiel, 12 miles from Dunedin, 81 per cent. of the children had given positive Schick reactions, and even in Dunedin City itself 70 per cent. of the day-school children were susceptible Schick reactors. In the Dunedin orphan institutions the percentage positive was 35. Considering the almost complete absence of diphtheria previous to 1926 and the exceptionally isolated character of the Kaitangata community, it was expected that the percentage of positive Schick reactors would be at least 80. In addition to this unusually low percentage, the positive reactions that did appear, were very much fainter and less extensive than had been produced on previous occasions by the same batch of toxin. Moreover, only two pseudo-reactions were recorded among the 206 subjects who had been read as negative reactors. According to general experience, such a low percentage of pseudo-reactions is only seen in a community with a large proportion of Schick susceptibles. Thus this scarcity of pseudo-reactions indicated that the herd immunity was very low, while the specific Schick reactor itself indicated a relatively high degree of immunity.

One hundred and eighteen of those children who gave a positive Schick reaction were given three doses of toxin-antitoxin mixture at weekly intervals. The prophylactic was supplied from the Commonwealth Serum Laboratories, each c.c. of the prophylactic contained one unit of antitoxin and 0·8 of an L + dose of diphtheria toxin. The doses given of this mixture were $\frac{1}{8}$, $\frac{1}{4}$ and $\frac{1}{2}$ c.c. The toxin-antitoxin mixture was stored in 10 c.c. glass ampoules and all unused solution in opened ampoules was discarded at the end of each day. There was a notable absence of local and constitutional disturbance, except in the case of a school mistress who gave a slight local reaction which lasted for three days.

6. Deterioration of Schick toxin.

The unusual faintness of the reactions and the anomalous results of the Schick testing in April roused suspicions that the test toxin had lost potency. On return to Dunedin from Kaitangata these suspicions were confirmed. A subject, who was known to be a sensitive positive reactor and who gave no pseudo-reaction, was tested with freshly diluted toxin in a $\frac{1}{2}$ and $\frac{1}{10}$ the standard doses. The half dose gave a reaction the size of half-a-crown desquamating at the end of a week and still evident after a month had passed. The tenth dose gave a reaction the size of a shilling which did not desquamate but was visible

[1] Zingher, A. (1916), *Amer. J. Dis. Child.* **11**, 269.

[2] Medical Research Council (1923), *Diphtheria*, London, p. 362.

for 14 days. This subject, when treated with a full dose of the diluted toxin which had been used 4 days previously at Kaitangata, only gave a faint reaction which began to fade in 48 hours and had disappeared within a week. It might appear probable that keeping the diluted toxin in a cupboard for 4 days at room temperature would suffice to explain the loss of potency, but Glenny, Allen and O'Brien[1] state that after 7 days at 15° C. the loss in potency is just detectable in diluted toxin.

Further experiments were carried out to endeavour to determine what factor, or factors, were responsible for the deterioration in the potency of toxin. Freshly diluted toxin was taken to Kaitangata under exactly similar conditions as before, and a maximum thermometer was placed in the carrier. The temperature recorded was 30° C. The toxin was then tested out on known positive reactors using at the same time freshly diluted toxin as a control. The results showed in each case a faint positive with the experimental toxin and a stronger positive with the freshly diluted toxin.

Tests were also carried out in the laboratory with (*a*) diluted toxin kept at room temperature for 2 days, (*b*) with diluted toxin which had been in the vaccine shaker for an hour, and (*c*) with freshly diluted toxin. The toxins were tested out on known Schick-positive reactors and showed strong positive reactions in (*a*) and (*c*), and negative reactions in (*b*).

It is evident, therefore, that the principal factor in the deterioration of the toxin was the shaking to which the diluted toxin had been subjected in a motor journey of 52 miles. The hydrogen-ion concentration of the saline was 7·8, and as acid solutions are detrimental to the toxin it might have been wiser to use a definitely alkaline reagent of *p*H 8. This factor, while not as a rule important, may assume importance when the toxin is exposed to shaking. Such accidents can be avoided nowadays by the use of a buffered diluent such as O'Brien, Okell and Parish[2] have described.

This definite demonstration of the loss of potency in the toxin used in the original Schick reaction was disconcerting, but the repetition of the Schick test on the negative reactors was not practicable at the moment. However, the error was the same for all the children, and though many of the negative reactors were undoubtedly below the Schick standard of immunity, it was felt that the immunity of the population would be raised to a reasonably safe level, both by the epidemic itself, and by the active immunity which the prophylactic innoculations were expected to confer on the positive reactors. The fact that the population was a remarkably stationary one was theoretically also in favour of this assumption, since the work of Topley and Wilson[3] suggest that a community is more likely to remain free from an epidemic if fresh susceptibles are not being added to it.

[1] Glenny, A. T., Allen, K. and O'Brien, R. A. (1921), *Lancet*, i. 1236.
[2] O'Brien, R. A., Okell, C. C., and Parish, H. J. (1928), *Public Health*, **41**, 181.
[3] Topley, W. C. C. and Wilson, C. S. (1923), *J. of Hygiene*, **21**, 243.

7. The Schick immunity in November.

These theoretical expectations concerning the immunity of Kaitangata to diphtheria were shattered by the appearance of the October epidemic. It was therefore decided to continue the Schick test investigation. In November 48 children, who had given negative reactions to the weak toxin used in April, were retested. The test toxin this time was diluted at Kaitangata. These November results have been embodied in Table IV, col. 6, in order that they may be compared with the April Schick tests. Thirty-three or 69 per cent. of these retests on children, who had been previously recorded negative, now were read positive. On the assumption that these new figures were representative, the original percentage of positive reactors in April would, if a fully potent test toxin had been used, been 81 instead of 40 per cent. (see Table IV, col. 9). In addition to these 48 retests 20 children who had never been tested before produced 13 (65 per cent.) positive reactions, a further demonstration that the original Schick test immunity figure for Kaitangata was far too high. If these two samples are combined, and 19 positive reactions are added to allow for the 40 per cent. which were originally recorded positive with the weak toxin, it can be assumed that *at least* 65 out of 87 should have been recorded as positive in April, because it is not unreasonable to suppose that the antigenic stimulus of the April-May diphtheria epidemic would have increased, rather than diminished, the immunity of the children. Therefore a susceptibility to fully potent toxin of 75 $\pm$ 4 per cent. deduced from tests in November is, on these grounds, more likely to be a low than high estimate of the true Schick positive percentage in April. If Table IV is re-examined, it is seen that neither the April, November, nor corrected Schick results, give any indication of an increasing immunity with age, such as is invariably found in populous areas where diphtheria is endemic. Actually in this case the eldest group (10–15) is the most Schick susceptible, but the difference between the figures is too small to have any significance. It is a great pity a fair sample of adults could not have been included for comparison, for while the children for the most part were born and bred in Kaitangata, many of the adults had emigrated there, and hence should have been more immune. This inference is supported by the relative attack rates among subjects over and under 15 being 2·1 and 12 per cent. respectively. The absence of an immunity age gradient in the children is to some extent confirmed by the morbidity rates shown in the last column of Table IV. Dudley[1] pointed out, with regard to some statistics from Baltimore, that although, as usual, the morbidity per 1000 of the population was as great, or greater, in the 0–5 age group, yet if the morbidity was calculated per 1000 Schick susceptibles the attack rate was greater in the early school ages of 5–10. This indicated that the school was really a more favourable environment than the home for microbic dissemination; but that in towns this advantage was masked by the greater susceptibility of the

[1] Dudley, S. F. (1929), *Quart. J. of Med.* **22**, 334.

pre-school age group. In the unsalted community of Kaitangata, there being apparently little difference between the Schick immunity of the pre-school and the school-age group, the more infective nature of the school environment is reflected in the higher incidence of diphtheria in the school-age groups. Although the Schick tests do not suggest that the senior or older members of the school were more immune, yet their morbidity was lower as Table V shows.

Table V. *Age distribution of diphtheria among the school children.*

Age group	Average no. in group	Incidence of clinical diphtheria: April and March No.	April and March %	Oct. and Nov. No.	Oct. and Nov. %	Total No.	Total %
5–10	190	19	10 ±1·4	17	9 ±1·4	36	19 ±1·9
11–15	190	14	7·4	6	3·2	20	10·6
5–15	380	33	8·7±1·0	23	6·1±0·8	56	14·8±1·2

The difference between the incidence in the 5–10 age group and the total morbidity (5–15 group):

In April and March was 1·3 < 1·7 its probable error
In Oct. and Nov. „ 2·9 < twice 1·6 „ „ „
In both outbreaks „ 4·2 < „ 2·2 „ „ „

This distribution might have been due to chance and not necessarily due to any real difference, such as the susceptibility to diphtheria, between the older and younger school children.

The differences in the attack rates which are given in Table V are however scarcely significant. But if the data in Table V are considered in relation to Table II, which shows that 13 out of 23 of the school children attacked in October and November were in the lowest standard of the school, the probability becomes greater that the higher morbidity of the 5–10 age group was due to some factor which was not operative, or was less effective, in the 11–15 group. During the 6 months' interval between the two diphtheria outbreaks an unknown number of fresh infants had joined the primary standard. These new entries would be more susceptible to diphtheria than those children already at school who had experienced the immunising effect of the first outbreak, and it is conceivable that the addition of fresh susceptibles to the primary standard was a factor which increased the attack rate in this group. If this were so it would be analogous to the well-known phenomenon, demonstrated originally by Topley[1], for mouse typhoid, namely, that the addition of fresh susceptibles to a herd of mice in the presence of *B. aertrycke* is followed by an increase in mortality of the whole group.

8. The November incidence in relation to the immunological findings in April.

The results of retesting children in November indicated that over 60 per cent. of the children, who had not reacted to the deteriorated toxin, which was used in April, would have given positive reactions if a fully potent Schick toxin had been employed. It was, however, hoped that the weak toxin

[1] Topley, W. C. C. (1919), Goulstonian Lectures, *Lancet*, ii. 91.

had picked out the most susceptible reactors, and that, since those reactors had been inoculated, they would show a lower attack rate in the spring milk-borne epidemic. Also it was expected that the children, who had given negative Schick tests with the deteriorated toxin, might yet have some degree of resistance to diphtheria even if the antitoxin titre of their blood was below ordinary Schick level (0·03 unit per c.c.) and that therefore this group would be more immune, on the average, than those children who had neither been tested nor inoculated with a prophylactic. The population, supplied with the milk which was presumed to be infected, was divided up in the way shown in Table VI.

Table VI. *November distribution of diphtheria among the school and pre-school ages according to immunological history in April.*

(Contaminated milk users only.)

	Pre-school 0–5			School age 5–15			Total 0–15		
April history	No. in group	Diphtheria cases No.	Diphtheria cases %	No. in group	Diphtheria cases No.	Diphtheria cases %	No. in group	Diphtheria cases No.	Diphtheria cases %
S –	9	2	*22*	31	13	42 ± 5·8	40	15	38 ± 5·3
IS +	12	3	*25*	28	4	14	40	7	18
S ±	26	6	*23*	23	4	17	49	10	20
Totals	47	11	*23*	82	21	26 ± 2·0	129	32	25 ± 2·5

S – ≡ No reaction to weak toxin used in April.
IS + ≡ Schick positive (April) and inoculated with toxin-antitoxin.
S ± ≡ Neither Schick tested nor protected in April.

The only marked divergence from the average morbidity is seen in the S – school-age group. This difference is (42 – 26) 16 which is 2·6 times 6·2 its probable error. Or if the whole S – group is taken, the respective morbidity is 38 per cent. compared with 25 per cent. for all those scholars who were supplied with milk from vendor A. (see Table III). The average error now becomes 5·8, which is just under half 13, the difference. The figures are barely significant that the S – group were more susceptible than, or otherwise different to, the "protected" IS + group. Moreover, the S ± group which would be expected to have been the most susceptible group, because this group must have included many very sensitive reactors of the type which were "protected" in the IS + group, suffered from an attack rate which was practically identical with that of the protected IS + group.

It is seen that the inoculated group (IS +) produced the least number of cases, and that the difference between the morbidity of this group and that of the weak Schick negatives is suggestive of a higher herd immunity in the inoculated. This surmise is, however, discounted by the fact that the group, which had been neither tested nor inoculated in April, and should therefore have been the most susceptible sample, had an attack rate that was practically as low as that of the inoculated and, theoretically, most immune group. When the samples are subdivided into pre-school and school ages, the only sample which shows an attack rate which varies much from the average is the weak Schick negative (S –) school group. The 13 patients in this group were mainly from the primary standard (see Table II, October-November columns), and perhaps one or two of these contracted infection in the class room of the primary standard and were not infected by milk. Taken as a whole, Table VI suggests that the prophylactic course of injections in April had had little or no

protective effect. On the other hand, those who reacted to the deteriorated toxin in April were probably at the time the most susceptible group, and it can be argued that the course of toxin-antitoxin mixture which they received in April had raised the immunity of the group as a whole up to, even if not above, the average level of the whole population, since in October and November they showed an attack rate lower than the average. In October and November, 16 cases occurred amongst those subjects who had given negative reactions to the deteriorated toxin in contrast to 8, who had been inoculated because they had had Schick positive reactions in April. Although there was one fatal case (a child of $3\frac{1}{2}$ years old), yet these two groups of patients had on the whole less severe attacks than the 22 cases who had neither been tested nor immunised. This latter group probably included some very susceptible reactors who might have reacted even to the weak toxin used in April, and would in that case have been given a course of toxin-antitoxin. These 22 patients included 12 adults, of which the milkman, aged 47, who supplied the suspected milk, was the eldest. Most of these patients suffered from severe symptoms and two died. This contrast in severity hints that those who were feebly Schick negative in April and those who had been inoculated, while not significantly more immune from attack, yet once attacked had a degree of resistance which enabled them to respond with a less severe reaction or illness than the average of the whole population. A surmise which is strengthened by the experiment described in section 10.

9. The results of a retest on inoculated children.

Sixty-five of those children who had been given a course of toxin-antitoxin inoculations in April were retested in November. During the seven months which had elapsed, since this attempt to stimulate active immunity, only 18 subjects developed enough antitoxin in their blood to make a Schick test negative. This is further indirect evidence that the proportion of positive Schick reactors which was found in Kaitangata by use of the weak toxin in April was much too low. It has been shown by many observers, such as Zingher[1], O'Brien, Okell and Parish[2] and Dudley[3] that the higher the original immunity of a population the more rapid becomes the induction of active immunity by diphtheria antigens. In the authors' own experience, the percentage of Schick immunes was 65 in the orphanage institutions of Dunedin; and among these active immunisation was successful in producing negative reactions in all of the 35 per cent. of Schick susceptibles within 16 weeks. On the other hand, in the rural district of Mosgiel, where 20 per cent. of the children were Schick immune, only 38 per cent. of the 80 per cent. susceptible children had changed their Schick reaction from positive to negative when retested four months after a course of toxin-antitoxin

[1] Zingher, A. (1922), *J. Am. Med. Assoc.* **78**, 1945.
[2] O'Brien, R. A., Okell, C. C. and Parish, H. J. (1929), *Lancet*, i. 149.
[3] Dudley, S. F. (1928), *Brit. J. Exp. Path.* **9**, 290.

inoculations. For these reasons the fact that in Kaitangata only 28 per cent. became negative reactors in 7 months is corroborative evidence that the original herd immunity must have been very low. It should, however, be noted that this figure is not strictly comparable with the corresponding 38 per cent. who became immune in 4 months at Mosgiel, because the deteriorated toxin used in April to test the Kaitangata children probably selected only the exceptionally susceptible reactors, who would naturally be harder to immunise than a group which had been selected by means of a fully potent toxin.

10. Primary and secondary antigenic stimuli in the human subject.

Glenny and Sudmersen[1] showed that the injection of diphtheria toxin into an animal not only stimulates the production of antitoxin, but also increases the power of the animal to produce antitoxin rapidly when submitted to a subsequent dose of toxin. Thus if a dose of toxin is given to an animal, who has no antitoxin in its blood, and has had no previous contact with toxin, the development of antitoxin is feeble and slow. A stimulus followed by this type of response is termed "primary." If however there are minute quantities of antitoxin already present in the blood, or the animal has had at some time previously a dose of diphtheria toxin, the exhibition of another dose of toxin is followed by a markedly increased and rapid production of diphtheria antitoxin, which is the typical response to a "secondary stimulus." On the assumption that the human response might be the same as that of experimental animals, it was expected that those children who had received inoculations of toxin-antitoxin in April, although still retaining their positive Schick reactions, would respond more rapidly to a further small dose of diphtheria antigen than those susceptible reactors, who had not had the benefit of the primary prophylactic injections during the previous April. In order to test the truth of this hypothesis, two samples of children whose Schick reactions were all positive in November were each given 0·25 c.c. of toxin antitoxin mixture per child. These samples were retested 7 days after the inoculation. The results are shown in Table VII, which is a most interesting confirmation of Glenny's work, using human subjects instead of the ordinary experimental animals. The November dose of antigen (including the Schick dose of toxin) acted as a secondary stimulus to 66 per cent. of the group who had received a primary stimulus in April, whereas in the case of the sample of children, who had never before received an artificial stimulus, only two reactions changed from positive to negative during the course of the week. It is probable that these two children had received a natural "primary stimulus" from the diphtheria bacilli in their environment. In addition to the above groups, 4 children who had had diphtheria but were Schick positive were given 0·25 c.c. of prophylactic. Seven days later two of the reactions had become negative. Moreover, among 9 children with histories of recent diphtheria, 7 had positive Schick

[1] Glenny, A. T. and Sudmersen, H. C. (1921), *J. of Hygiene*, **20**, 176.

Table VII. *The response to secondary and primary stimuli in the human subject.*

	History of children all of whom had positive Schick tests in November	Number in group	No. remaining Schick + 7 days after $\frac{1}{4}$ c.c. toxin-antitoxin in November	
			No.	%
A.	Inoculated in April	41	$14 \pm 2{\cdot}0$	34 ± 5
B.	Not inoculated until November	31	$29 \pm 0{\cdot}9$	94 ± 3
C.	Total	71	$43 \pm 2{\cdot}8$	61 ± 4

The percentage difference between the previously stimulated group A and the total sample C is $61 - 34 = 27$, which is 4·2 times its probable error 6·4. Group A therefore possessed a greater power of response to the antigen administered in November than Group B which had received no primary artificial antigenic stimulus six months previously.

tests, which confirms the now well-established observation that, either an attack of clinical diphtheria is often a poor antigenic stimulus, or that clinical diphtheria only attacks those whose "power to respond" is abnormally weak. It is noteworthy that Table VII indirectly supports the suggestion that the milder type of infection and the lower incidence of disease among the previously inoculated, though Schick positive reactors, discussed in section 8, was a real phenomenon due to an augmented immunity rather than to chance in sampling.

11. The effect of the April outbreak on herd immunity.

These two outbreaks of diphtheria in a remote community raise a very interesting question: Did the autumn epidemic increase the resistance of the community as a whole to the spread of diphtheria infection? At first sight the March-April outbreak would appear to have had no effect on the herd immunity of Kaitangata, because in the subsequent spring the incidence and severity of diphtheria was just as great, if not greater, than in the preceding autumn. But the methods of dissemination were different in the two epidemics. In March and April the infection was undoubtedly air-borne and took place chiefly in the school class rooms. In October and November milk was probably responsible for the majority of infections. The difference in the incidence, among the school children who had drunk suspected milk, and those who were not known to have done so, is most striking. Among 80 children attending school who had milk from the contaminated source 20 got diphtheria, of the remaining 300 only 2 were clinically infected. Thus the ratio of morbidity of the drinkers of suspected milk to that of the rest of the school was over 35 to 1. Table II shows that although cases of diphtheria were notified from every class room in October and November yet diphtheria did not spread, except in two cases, to those who, as far as is known, did not drink infected milk. It seems hard not to believe that the herd immunity of the school had been raised to such a pitch by the first epidemic, that the ordinary means of spread by droplet infection had become much more difficult in the second outbreak, but that this degree of herd immunity was insufficient to resist massive doses of infection in contaminated milk. The ratio of infected households to infected

individuals was practically the same in both outbreaks. In the autumn 34 households produced 45 cases, which implies that not more than 11 subjects could have been infected at home from a previous patient in the same family. In October and November 34 houses received the suspected milk which infected 46 of their inhabitants, therefore not more than 12 households can have produced multiple cases. A common characteristic of milk-borne infection is the simultaneous onset of symptoms in several members of one family. It is seen in Kaitangata that this characteristic was not very marked in the milk-borne epidemic. May it not be that the previous outbreak, by raising the herd immunity, had masked this effect? That is to say, the incidence in families supplied with infected milk would have been greater if some of their members had not had their immunity raised by exposure in the previous autumn to the air-borne school epidemic. Such arguments support the inference that, in spite of the greater severity and similar morbidity of the second outbreak, the first outbreak had augmented the herd immunity of Kaitangata.

12. Summary and conclusions.

1. The incidence produced during 1926 by two epidemics of diphtheria, in a remote and unsalted country district, was equivalent to 30 years of the London endemic morbidity.

2. The cases arose in two distinct groups. An autumn outbreak with a definite concentration of infection on the school age, and probably disseminated by droplet infection, followed by an epidemic in the succeeding spring which was more severe, probably milk-borne, and in which the frequency of cases was higher among infants and adults than school children.

3. The effect of a long drive over bad roads caused a deterioration of the diluted toxin which was used for a Schick test investigation. The use of this toxin led at first to false conclusions regarding the immunity of the children, since it only caused reactions in the most susceptible members of the community.

4. As a result of retesting with a fully potent toxin it was estimated that the figure of 40 per cent. susceptible which was found with the weak toxin would have been about 80, if full strength toxin had been used.

5. The attempt to immunise actively those children who had reacted to the weak Schick toxin was found to have failed in 72 per cent. of a group which was retested 7 months later. The prophylactic course was identical with one which had succeeded in inducing Schick immunity, within 4 months, in 100 per cent. of the susceptible children in the Dunedin orphanages.

6. The slow rate of immunisation at Kaitangata is attributed to two causes, (*a*) the low original herd immunity of the district, (*b*) the selection by the weak toxin of only the most sensitive reactors which were almost certainly the most "unresponsive" members of the total Schick positive population.

7. By a comparison of the rate of response to a small dose of toxin-antitoxin mixture, in those positive Schick reactors (*a*) who had, and (*b*) who had

not, received previous prophylactic injections, it was shown that the principle of "primary and secondary" antigenic stimuli held good for human subjects, as well as for experimental animals.

8. Careful examination of the known data led to the conclusion that the air-borne autumn epidemic had increased the herd immunity of the population, in spite of the fact that the subsequent milk-borne spring outbreak produced as high a morbidity and a more severe type of diphtheria.

9. The practical lessons which may be learnt from this study are: (*a*) That unless a special buffered diluent is used, the toxin used for Schick testing must be freshly diluted near the place where it is to be used. (*b*) Active immunisation of remote unsalted communities against diphtheria requires more time, and more intensive courses of prophylactic, than areas where diphtheria has been endemic for some years. (*c*) In such places with a low original herd immunity, it is essential, even more than in endemic centres, never to omit retesting those who have been inoculated, in order to be certain that any attempt made to induce active immunity to diphtheria may be successful. (*d*) Estimations of the relative efficiency of diphtheria prophylactics, which are based on the rapidity with which samples of children become immune, are worthless unless all the observations have been made in the same environment on groups having the same original herd immunity. (*e*) An immunity, good enough to withstand droplet infection in a day school environment, may be broken down by massive doses of diphtheria bacilli in milk.

10. The study of outbreaks of disease in communities which are not too large to prevent a complete supervision of the whole population and environment, enable one to visualise imaginary mechanisms of infection very much more easily than in large populous areas, where so many more factors have to be left unexamined, or remain unsuspected. The hypotheses, perhaps better termed surmises, which the facts suggest, are only intended to be purely tentative and temporary. Their practical value is that they indicate to the investigator a plan of campaign and suggest what to look for, in the lucky event of his ever again meeting with a similar combination of circumstances. In epidemiology in general, as illustrated by this particular instance, opportunities arise and pass, often never to recur, and much is missed, or left undone that might have been done, if only the knowledge and hints gained during the passage of the epidemic itself had been known before its advent.

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