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Infectiousness and Immunity in Regard to Chickenpox, Whooping-cough, Diphtheria, Scarlet Fever and Measles.

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Introduction.—A survey of the pronouncements of epidemiologists as to what is the most important factor in the control of epidemics leaves one with the impression that these exhibit to a remarkable degree at least two of the characteristics of the phenomena of which they treat, namely, variability and periodicity. I do not propose to follow the well-trod path back to Sydenham to prove that there has been a succession of cycles in which the emphasis has alternated from the infecting agent—subject now to its biological modifications, cycles of development, or changes in virulence, and now to the mysterious influences of epidemic constitutions, through obscure atmospheric and seasonal states—to the attacked population, with its changing susceptibilities and immunities, and then back again to the virus, for which new and remarkable properties have in the meantime been postulated. The last swing of the pendulum seems of recent years to have brought us very rapidly and unmistakably again to the viewpoint that immunity is the most interesting and perhaps the most important of the factors concerned in the mechanism of epidemics.

For this we have to thank the combined labours of investigators in several different fields. The field work of Glover [1] on the behaviour of cerebrospinal fever and the careful cartographical work of Wickman and Wernstedt [2] on the Swedish epidemics of acute poliomyelitis in 1905 and 1910-13 indicated that in the control of epidemics of these diseases at least immunity is the most important factor. The observations of public health workers who have been applying the immunological methods evolved by Schick and the Dicks have proved almost beyond doubt that processes of latent immunization are responsible for protecting very large sections of the population against diphtheria and scarlet fever, and the careful and ingenious researches of Dudley [3] on the behaviour of a small enclosed population have thrown much light upon the mechanism by which this is brought about. The team work of the experimental and statistical epidemiologists, Topley and Greenwood [4], have also proved that immunity acquired, without contracting the disease, by exposure to infection from pasteurellosis and mouse typhoid is an important factor in the control of epidemics of those diseases in populations of mice. Finally, the work of Gill [5] on the spleen rate in populations exposed to epidemics of malaria has brought to light evidence of wholesale immunity acquired during epidemics by natural processes, without clinical illness, which then gradually subsides before another epidemic can occur.

In considering the periodicity so characteristic of measles in urban areas, which had furnished such fascinating material for study at the hands of Munro [6], Whitelegge [7], Hamer [8] and Brownlee [9], Gill's work suggested to me that a process of latent immunization, not permanent as seems to be the case in diphtheria, but slowly disappearing as in malaria, might explain why the amplitude of rise and fall in the proportions of children protected by a previous attack of measles in a population is too small to be regarded as the chief cause of the periodicity. That it is too small was proved by a laborious analysis of the notification records in St. Pancras, and in support of the theory of a temporary latent immunization of the

population gradually lost again over a period of two or three years, I was able to publish some evidence more than a year ago [11] and to amplify it in a more recent paper [21].

And if latent epidemization be an important factor in diphtheria, scarlet fever, cerebrospinal fever, acute poliomyelitis, malaria and perhaps measles, might it not also be of importance in whooping-cough, smallpox, chickenpox, German measles and mumps?

In taking up this line of study it was of course obvious that there were great difficulties ahead, because the only method of measuring immunity of individuals to this group of diseases at present is by observing whether these individuals do or do not contract the diseases when exposed to infection in the ordinary course of events, that is to say, the weapons of research in this field are purely statistical. Reliance must also be placed upon the data made available by the compulsory notification of these diseases in certain local areas. In districts such as St. Pancras and Paddington, where compulsory notification of measles has been in force for years, I have satisfied myself that notification data are free from any bias likely seriously to influence statistical conclusions, except in two respects, which must be kept in mind: (1) that a possible margin of about 15%[1] must be allowed for those who escape notification, and (2) that there is some inevitable confusion with German measles during epidemics of that disease.

A careful analysis of histories in regard to several infectious diseases has recently been made by Collins [13], based upon very large numbers of school children, college students and others in fifteen localities in the United States of America. In this paper catalytic curves have been fitted to the data after division into years of age, and these show that 89% of children have measles, 52% have chicken-pox, 11½% have scarlet fever and 10% have diphtheria, on the average, in those localities by the seventeenth year of life. Allowing for German measles in the total it seems a fair conclusion that about 85% of children in the mixed population of a large town have measles at some time during life.[2] A calculation from the records in Paddington later in this paper shows that about 40% of children born are likely to be notified for chicken-pox, and comparison with the figure of 52% obtained by Collins from histories suggests that the notified and reported cases in Paddington represent the bulk of the cases occurring.

Statistical evidence for latent immunization—methods of approach.—There are two methods by which immunity changes in a population may be studied by means of notification records: (*a*) by measuring the apparent infectiousness of cases of the disease at different periods of time, and (*b*) by actually following up contacts intimately exposed to infection and comparing their subsequent behaviour with control groups not so intimately exposed.

(*a*) *Apparent infectiousness.*—In his Milroy lectures in 1906 Hamer [8] made an analysis of the London measles wave, which was a delightful example of the application of simple mathematical processes to epidemiology, carried out with such clearness of exposition that a child could understand it. In this he supposed that the measles cases occurring in a given week arose directly from those occurring in the week but one previously, and pointed out that near the start of an epidemic wave four cases were giving rise to five on this basis, whereas near the end five were giving rise to four, and on the assumption that this change was entirely due to the reduction of susceptibles in the population he proceeded to equate these changes to the cases during the epidemic and the influx of susceptibles by births, and thus arrived at an estimate of the numbers of susceptibles in the

1 I have shown [11] that in St. Pancras 70% of children are notified for measles before adult life, and since German measles is separately recorded, about 75% will be notified for one or other disease.

2 Butler [12] concluded that in Willesden about 97% of children attending public elementary schools had measles at some time, but this figure, as he admitted, was only applicable to the class of children selected, and it included, I think, German measles.

population. In the steady state, where weekly cases are neither increasing nor decreasing, as in an inter-epidemic period, one case infects one on these assumptions, and the fractions $\frac{5}{4}$ and $\frac{4}{5}$ might be regarded as indices of infectiousness, and, indeed, they have really been used as such in a recent more elaborate mathematical examination of Hamer's original assumptions in a paper by Soper to the Royal Statistical Society [10].

When we pass to Brownlee's [15] mathematical analysis of the epidemic curve, we find again the use of the incubation period as interval, and the assumption that all cases contracted their infection from other clinical cases which occurred at this interval further back in time; but the effect of changes in proportions of susceptibles in the population is now neglected, and the infectiousness, as it is evidenced by the rate of increase of cases, is equated to a rate of loss of infectivity of the infecting agent. The discovery of the importance of carriers and latent cases in infectious diseases makes it probable that the assumption made by both Hamer and Brownlee, that every clinical case arises directly from a previous clinical case, is not at all a safe one, even in general reasoning of this sort, for infection may be handed on by carriers or latent cases, which may be more numerous in proportion to actual cases at one period of the epidemic cycle than another. This assumption would certainly lead us astray in dealing with cerebrospinal fever and diphtheria, and it may also do so with measles and other diseases. It is also evident that one or both of the opposing assumptions, that the infecting power of the virus does not change, and that changes in this infectivity are all important, must be wrong. Thus far, then, no satisfactory measure of infectiousness had been devised, and the proposal of Stallybrass in a paper read before this Section [14] to introduce the term " index of dispersability " did not solve the difficulty, for it was once again the ratio between numbers of cases arising in successive intervals of time, which now had no relation to the incubation period.

An index of infectiousness was wanted which, whilst avoiding the assumption that there is no reservoir of infection other than clinical cases, and allowing for changes both in the facility of transmission from case to case, if this is subject to change, and in the proportion of non-immune persons present in the population, would at the same time be sufficiently simple to calculate to make it of practical use to public health workers not trained in mathematics. In my paper on the " Epidemiology of Measles " I defined such an index and termed it the *index of apparent infectiousness.*[3] It involves the definition of a " secondary case " for the purposes of the index, as a child of a defined age (A) who develops the disease at a defined interval of time (T) after a case (of any age) residing in the same house, the interval T being chosen to embrace most of the possible range in the incubation period. As an example, for measles A has been taken to include all ages under 10 years, and the interval T to be ten, eleven, twelve or thirteen days between appearance of the rash in the two cases, the reason for this selection being made clear in the distribution of 3,450 such intervals in Table 1. Where a case arises *in the same house* ten to thirteen days after a previous case, the probability that it was not due to direct infection but to the agency of some source of infection outside the house, may be regarded as so small as to be quite negligible, although the probability that the first case arose from a carrier and not a clinical case may be quite considerable. By thus standardizing the conditions of exposure by restricting them to those involved in residence in the same house as a case, the difficulty of the possibility of important reservoirs of infection existing other than clinical cases is got rid of, and moreover it enables us, as I shall show, to obtain an index of infectiousness far more sensitive than Hamer's ratio.

With this as definition of a " secondary case " the apparent infectiousness during any given period is measured by the ratio p of the number of secondary cases[3] s arising from them to the total cases n occurring during the period. Whether these

[3] For a full exposition see Reference No. 11, pp. 389-390.

secondary cases all occur within the period studied or not is immaterial; the infection may be assumed to have been transmitted to children living in the house within a few days of the onset of the first case, and it is the intensity of this infecting process which is being measured, so that the dates of onset of the secondary cases need not be considered so long as the interval is right. Thus the infectiousness during the first week of March for measles would be given by the total cases developing the rash in that week divided into the secondary cases to them, which, according to the definition, might develop the rash on any date from March 11 to March 20, but would presumably have received their infecting doses during the first week. This ratio $p = s/n$ being dependent upon such local factors as average size of family and conditions of overcrowding, in order to obtain an index comparable from one area to another, the ratio is best expressed in terms of its value p_o during a post-epidemic period, when incidence is steady and at a low level, as unit.

The resulting *index of apparent infectiousness* p/p_o is the product of two other indices not so readily measured, namely the *index of true infectiousness* or relative facility of transmission from person to person [4], which is subject to sudden fluctuations as we shall see, and the *index of communal susceptibility*, which is the proportion of the population aged A susceptible to the disease at the middle of the period in terms of the proportion susceptible at the middle of the standard post-epidemic period.

To take an example, suppose that in a town of 600,000 population, of whom 100,000 were children under 10, there occurred in the month of January in an epidemic year 1,000 cases of measles, and that in the houses where these occurred there followed 120 cases aged under 10 with an interval of ten, eleven, twelve or thirteen days between the appearance of the rash in the two successive cases. Then 120/1000 or ·12 will represent the apparent infectiousness p during January, and in order to turn this into an index we express it in terms of p_o for a post epidemic period when incidence was stationary. For this purpose it is advisable to choose a longer period than a month, since the numbers of cases per month in such a period may be small and that of secondary cases will be still smaller. Let us suppose, then, that in the four months August to November there occurred 500 cases, followed by twelve secondary cases as defined, then 12/500 or ·024 represents the apparent infectiousness p_o, and using this as unit we find the index of apparent infectiousness p/p_o in January to be ·12/·024 or 5 exactly. This means that the probability of being followed by another case aged under 10 in the same house after the specified interval was five times as great at the beginning of the epidemic as in the quiet period following the epidemic. Now part of this is certainly due to a greater proportion of the children exposed being susceptible in the first instance than in the second. Let us suppose that 75,000 of the 100,000 children were susceptible in mid January, and only 30,000 remained susceptible at the middle of the post-epidemic period, then the *index of communal susceptibility* in January would be ·75/·30 or 2·5, and this would account for a 2½-fold increase in the apparent infectiousness, whereas a fivefold increase was actually found. We should then have to assume that the remainder of the increase was due to a real increase in the facility of transmission of the virus from case to contact, which I have termed the *index of true infectiousness*.

The equation connecting the three indices is the simple one:—

$$\text{Index of apparent infectiousness} = \text{Index of communal susceptibility} \times \text{Index of true infectiousness}$$

and in the example given the index of true infectiousness would be 5/2·5, or exactly 2, implying a twofold increase in the facility of transmission of the virus at the start of the epidemic as compared with its value in the post-epidemic period.

The index of apparent infectiousness is very easily measured by merely sorting the notification forms into alphabetical order of streets, bringing together all pairs of cases occurring in the same house with the specified interval between the onsets and

[4] This is really what Brownlee called "infectivity," and some have called "virulence."

with the specified age of the second case, and it has the advantage that it can be calculated for any period whatever according to convenience, which need not be restricted to calendar months or other arbitrary units having no relation to the epidemic phenomena. The behaviour of this index, considered in relation to the epidemic curve, can by itself tell us something about what is happening to the factors of which it is a product, for we can safely, I think, make certain inferences such as: (1) that the immunity of a population does not change in a sudden or explosive manner, and hence such sudden fluctuations in the index as are statistically significant must be attributed to changes in facility of transmission,[5] and (2) that a gradual rise in the index continuing over years without reference to seasonal influences is almost certainly due to changes in the immunity index. In order to obtain a reliable quantitative measure of the changes in the two component factors it is necessary to supplement the information secured from the composite index by some other methods of measuring immunity changes in the population, which will now be described.

(*b*) *Immunity of contacts.*—There are several possibilities to be considered: (1) that immunity is only attained by a clinical attack; (2) that an appreciable proportion, y, of children born, retain an inherent immunity to the disease; (3) that there is a latent immunization of a permanent character of x persons on the average to every notified case; (4) that there is a latent immunization of a temporary character rendering x persons immune to every notified case in the first instance, but then disappearing according to some continuous law of decrease; or (5) a combination of (2) with either (3) or (4).

In the first of these events the changes in communal immunity can be directly measured by deducting notified cases (corrected if necessary for incomplete notification) and adding acquisitions by births, the index of communal susceptibility calculated and the other component index thus arrived at indirectly. The presence of inherent immunity must be inferred rather than proved if, having ruled out latent immunization by one of the methods which follow, it is found that contacts have no greater ultimate expectation of catching the disease than children of the same age in the population as a whole, meaning that a certain proportion of children born are destined to have the disease, if not sooner, then later. In the second or third events, if y or x can be estimated, the changes in communal immunity can be arrived at, in the second event, by deducting notifications and adding $(1 - y)$ times the survivors of the births, and in the third event by deducting $(1 + x)$ times the notifications and adding the survivors of the births. In the fourth event the question is more complicated, but if some simple law of decrease in the number of latent immunes remaining after the lapse of a given time can be assumed or deduced, it is not at all difficult of solution provided that the rate of disappearance r can be estimated.

The methods I have begun to use with a view to settling whether there is any latent immunization at all, and if so whether it can be regarded as permanent or temporary and what are the values of y, x, and r characteristic of each disease, consist in following up through the records of the schools and health departments contacts of certain ages known to have been exposed to infection from a case in the same house, and comparing the rates at which they fell victims to the disease during subsequent intervals of time with the same rates of attack in control groups of children living in the same area or attending the same schools. Several methods have been used, all based upon this principle; thus the control group may consist of all children at risk of the same ages in the general population, or of children of the same ages who have been contacts to some other disease. In order to combine all ages together, a method of standardization for age by applying a set of smoothed

[5] If evidence of this is thought necessary, a study of fig. 5 in Reference No. 21 will show that the sudden increases preceding the epidemic wave cannot represent immunity changes in the population attacked.

attack-rates at ages has been employed, and where necessary a correction applied for children lost to view by estimating the annual removal-rate by means of the annual deductions from the electoral register.

These methods will be illustrated in the work I shall now describe, but the results so far obtained must be regarded as only tentative and introductory to further work on the same lines.

Diphtheria and scarlet fever.—The changes in apparent infectiousness of diphtheria and scarlet fever in St. Pancras during the five years 1925-29 have been worked out for comparison with the other diseases. For access to the records I am indebted to the Medical Officer of Health, Dr. G. Sowden. The distributions of intervals between the onset of the disease in pairs of cases occurring in the same house are shown in Table I, and the range of intervals chosen for definition of a "secondary case" was three to twenty days for diphtheria and two to eleven days for scarlet fever, the age of the secondary case being restricted to under fifteen years in each instance.

TABLE I.—INTERVALS IN DAYS BETWEEN ONSET OF DISEASE IN PAIRS OF CASES OCCURRING IN SAME HOUSE

Days	Diphtheria (St. Pancras)	Scarlet fever (St. Pancras)	Measles (St. Pancras)	German measles (St. Pancras)	Whooping-cough §		Chickenpox (Paddington)
					Wandsworth	Holborn	
1	24	11	341	27	5	1	116
2	18	25	246	7	8	3	93
3	15	31	160	8	27	5	67
4	19	14	117	3	33	7	44
5	21	16	96	—	36	10	33
6	15	8	90	4	37	13	24
7	11	8	99	6	37	14	39
8	12	15	173	—	36	13	31
9	12	11	206	2	34	12	39
10	8	7	318	2	32	11	45
11	4	8	353	3	30	10	64
12	6	2	329	3	29	10	106
13	2	4	269	7	27	9	205
14	8	1	205	6	25	9	260
15	4	6	153	8	24	9	222
16	5	4	104	5	22	8	148
17	5	3	70	8	21	8	63
18	—	4	48	4	19	8	65
19	2	2	38	6	18	7	28
20	4	3	35	3	16	7	23
21	—	3	*	1	15	7	30
22	2	4	*	4	13	6	13
23	—	1	*	—	11	6	7
24	1	3	*	1	8	5	9
25	1	1	*	1	6	4	7
26	1	1	*	—	4	4	15
27	1	3	*	—	3	4	7
28	6	2	*	—	2	4	13
†	56	43	*	1	26	36	124

§ Smoothed distributions. † Four to twelve weeks. * Not analysed.

The notified cases of diphtheria during the five years numbered 1,806, and the secondary cases as defined numbered 121.

From December 29, 1924, to August 30, 1925, there were 335 cases in thirty-five weeks, or about ten per week, and these gave rise to thirty secondary cases, a ratio of 8·96%. In a period of lower incidence and low infectiousness, from August 2, 1926, to January 30, 1927, there were 195 cases in twenty-six weeks, or seven and a half per week, and these gave rise to only seven cases, a ratio of 3·59%. The difference of 5·37 ± 1·39 may be regarded as significant,[6] and the index of apparent infectiousness has been calculated for consecutive periods throughout the five years in terms of the value 3·59% as unit. The result appears in fig. 1, which shows also the mean cases per week in each calendar month. When the records begin in 1925 the index was 2·50 (viz., 8·96/3·59) with an incidence of about ten or eleven

CHANGES IN APPARENT INFECTIOUSNESS OF DIPHTHERIA AND SCARLET FEVER
ST PANCRAS. 1925-1929.

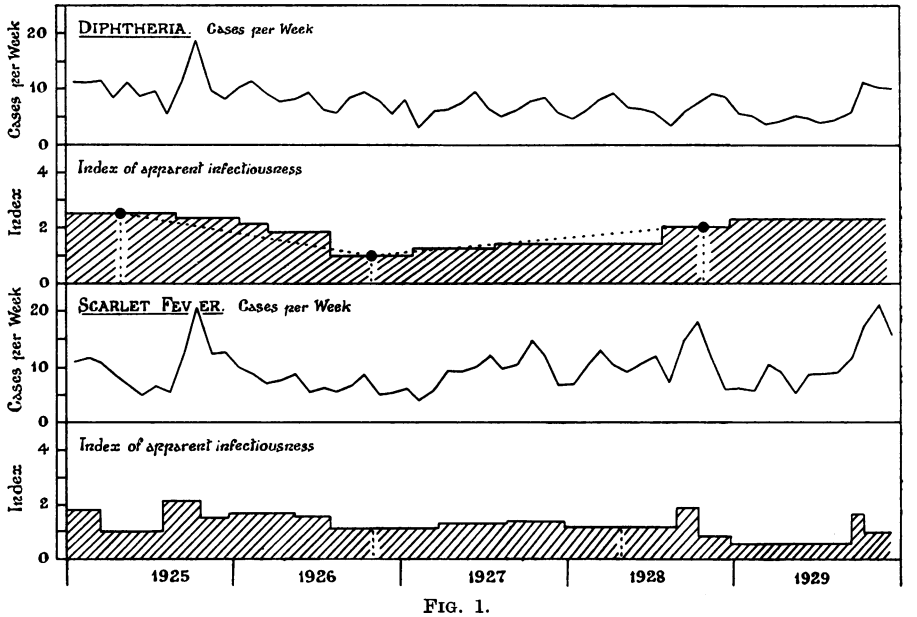

FIG. 1.

cases per week. A small autumn "outbreak" followed, with an incidence during October exceeding eighteen cases per week, and both incidence and apparent infectiousness then progressively declined to the autumn of 1926. During the next three years incidence remained low, averaging 6·3 cases per week, but the index of apparent infectiousness rose steadily from unity in the period August 2, 1926, to January 30, 1927, to 2·02 in the period July 30 to December 23, 1928, and to 2·27 during 1929. During the last three months of 1929 incidence was beginning to rise again, averaging eleven cases per week.

The first thing to notice is that no sudden fluctuations are evident in the index, such as we find in the other five diseases, but only gradual changes. The data here worked out are not nearly extensive enough to prove that such sudden changes,

6 These ratios relate only to the universe of affected houses, and the secondary cases which occur within this universe are not appreciably correlated with each other owing to their definition, hence the ordinary formula for random sampling has been used, here and subsequently in this paper. This could not, of course, be applied with safety to ordinary rates of incidence of an infectious disease.

occasioned, as they must surely be, by changes in true infectiousness rather than communal immunity, do not occur in diphtheria, but the contrast with the other diagrams suggests that they are not characteristic, and that this may be the reason why epidemics of an explosive character are also not characteristic of diphtheria. We may infer that the gradual changes in the composite index during 1925-29 were chiefly due to changes in the index of communal susceptibility. Let us assume they were entirely due to this and see where this leads by a simple calculation, proceeding from the facts indicated by the dotted lines in fig. 1, that the index was (*a*) two and a half times as great on May 1, 1925, as on November 1, 1926, and (*b*) twice as great on November 1, 1928, as on November 1, 1926, these dates being the middle of the periods for which the index was computed. During the first interval, whilst the communal susceptibility was falling, there occurred 746 cases in one and a half years, and during the second interval, whilst it was rising, there occurred 680 cases in two years. Since we know that latent epidemization must occur in diphtheria, let us suppose that each notified case was accompanied by x latent cases, and let M be the number of susceptibles on November 1, 1926, in the population at risk to attack by diphtheria during these years. The susceptibles were being replenished by fresh births, and we may arrive at perhaps the best rough approximation to this replenishment during any year, by deducting from the births in the previous year the deaths under one year of age, giving the survivors to one year who were being added to the population. On this basis the susceptibles added to the population during the first interval of one and a half years were 5,480, and during the second interval of two years 6,450, and if we assume that the whole population and all children born to it were at risk to infection, we obtain :—

(i) $746\,(1 + x) - 5{,}480$ = loss of susceptibles from May, 1925, to October, 1926 = $2\tfrac{1}{2}\,M - M = \tfrac{3}{2}\,M$.
(ii) $6450 - 680\,(1 + x)$ = gain in susceptibles from November, 1926, to October, 1928 = $2\,M - M = M$.

and equating these to eliminate M we get :—

$$746\,(1 + x) - 5480 = \tfrac{3}{2}\,[6450 - 680\,(1 + x)]$$

giving $x = 7\tfrac{1}{2}$ approximately.

This would mean that there are seven or eight immunizations to every clinical case notified in St. Pancras, and this certainly agrees with the estimate made by Frost [16] from Schick tests, that in the ordinary urban environment of Baltimore there were seven latent cases to each clinical case. I think, however, that this is an overestimate of x, for the assumption that *all* the children born into the population are going to be exposed to diphtheria infection, even in London, is not, I think, justified. For one thing, it leads to the conclusion that in November, 1926, only about 2% of all the children under 10 in St. Pancras were susceptible, which is scarcely credible. It has been proved conclusively that many children brought up in middle class homes remain Schick-positive, and most of these have presumably escaped exposure to the bacillus in any considerable doses. Let us suppose that in St. Pancras one-third of the families are sheltered from exposure to diphtheria and that one-third of the births are into such families; then if M^1 be the total susceptibles in the exposed families only on November 1, 1926, we get : $746\,(1 + x) - 3653 = M^1$, and $4300 - 680\,(1 + x) = M^1$ leading to $x = 4{\cdot}7$ and $M^1 = 410$; and, if we add to M^1 all the susceptibilities in the sheltered families, this means about 35% of the whole child population under 10 susceptible, which is not unreasonable.

A comparison of two curves by Collins [13] as representing the increase of Schick-negative children with age on the one hand and the proportion who had suffered from clinical diphtheria on the other in a very large mixed population in the United States of America shows 56 per cent. immunized and 9 per cent. who had had diphtheria by the fifteenth year, suggesting that $x = 5$, which agrees with the estimate of $4{\cdot}7$ above, and Dudley [3c] found a still lower ratio $x = 3$ for boys in

Greenwich Naval School, which he thought was to be expected owing to the exceptionally high infection pressure under dormitory conditions. Another point to be considered is that x may vary within certain limits even when communal immunity and other conditions are constant.

Turning now to *scarlet fever*, the incidence curve in fig. 1 shows an autumn outbreak in 1925, low incidence and no epidemic in 1926, a gradual rise of incidence in 1927 and autumn outbreaks in 1928 and 1929. Immediately preceding each of the autumn epidemics of 1925, 1928 and 1929, the index of apparent infectiousness rose suddenly to about twice its value in the post-epidemic periods. The period chosen as unit for computing the index was March 2 to August 1, 1925, when 119 cases occurred, followed by five secondary cases as defined in the same houses, a ratio of 4·20 per cent.[7] During the 1925 epidemic August 3 to October 25 there were 152 cases, followed by fourteen secondary cases, and during the 1928 epidemic September 3 to October 14 there were ninety-nine cases, followed by eight secondary cases, giving percentage ratios 9·21 and 8·08, or, if we combine these two, 8·76, which differs from the ratio in the period of lowest incidence December 26, 1928, to September 15, 1929, by $6{\cdot}15 \pm 1{\cdot}35$. We may therefore regard these rises as significant, and they doubtless indicate a sudden increase of true infectiousness due to a local upset of balance between the infection pressure factors and the immunity factors which was sufficient to start off an epidemic, though communal immunity was sufficiently high to prevent this going very far. Apparent infectiousness remained practically constant during the $1\frac{1}{2}$ years from November 1, 1926, to May 1, 1928, and in this period there were 723 cases. Since we have definite evidence that latent immunization occurs in scarlet fever, and also that a considerable proportion of children retain an immunity from birth which must be inherent, let us again suppose x latent cases to each clinical case, and that a proportion y of children retain an immunity after the first year of age. The replenishment of susceptibles by 4,902 survivors of the first year of age during the period gives an addition of 4,902 $(1-y)$, so that if all families are at risk from infection by scarlet fever,[8] and there is no change in true infectiousness, we have $723\ (1+x) = 4902\ (1-y)$ giving $(1+x) = 6{\cdot}8\ (1-y)$. Zingher's results from Dick tests on 7,700 children in New York [17] showed that about 28 per cent. appear to retain an inherent immunity at the end of the first year, giving $y = {\cdot}28$, and that by the fifteenth year another 52 per cent. had become Dick-negative. Collins' analysis of histories in American town populations [13] shows that by the fifteenth year 11 per cent. have suffered an attack of scarlet fever, which suggests in conjunction with Zingher's result that $x = (52-11)/11 = 3{\cdot}7$, and in that case $(1+x) = 4{\cdot}7$ and $(1-y) = {\cdot}72$, giving the equation $(1+x) = 6{\cdot}6\ (1-y)$ which is in remarkably close agreement with my own equation, derived solely from the index of infectiousness.

It may seem to some who have a distrust of statisticians that the agreement of these estimates for diphtheria and scarlet fever with those of workers using other methods is too good to be true and that the figures have been manipulated to produce agreement. I can only assure you that this is not so, and the reasonableness of the results thus obtained caused me some surprise, for the material and range of years so far analysed are obviously very inadequate. The analysis for these two diseases was undertaken to illustrate the possibilities of the method and in the hope of establishing some confidence in it by checking it against other data, before we proceed to those other diseases where no such data exist.

Probably the progressive decline in scarlet fever incidence over the last centuries has been accompanied by, or caused by, a progressive increase in y, the communal

7 A better period would have been the first eight months of 1929, with an apparent infectiousness of only 2·61 per cent., but the data for 1929 were not available when the diagram was drawn; it would merely alter the scale of the index.

8 This must be nearly true in towns since Dick tests show 80 or 90 per cent. immune by adult life is reached.

inherent immunity, and also in x, which measures the capacity of the population rapidly to acquire immunity without severe reaction when exposed to infection, a capacity which may also be inherited.

Whooping-cough.—Nearly thirty years ago Laing and Matthew Hay [18] made an analysis of over 20,000 notified cases of whooping-cough in Aberdeen from 1882-1900 and pointed out that in that city epidemics tended to be roughly biennial, whilst in Edinburgh there was more often a three-year interval, in Glasgow a three- or four-year interval, and in Dundee a four-year period. They also thought that high-peaked epidemics tended to be followed by longer periods of quiescence than lower-peaked epidemics.

Thanks to the kindness of the Medical Officers of Health of Wandsworth (Dr. F. G. Caley), and of Holborn (Dr. C. W. Hutt), I have been able to make some observations from the notification records of these boroughs during recent years. The Wandsworth data covered the three years 1926-28, during which time 4,204 cases were notified, and the mean weekly incidence and index of apparent infectiousness are shown in fig. 2.

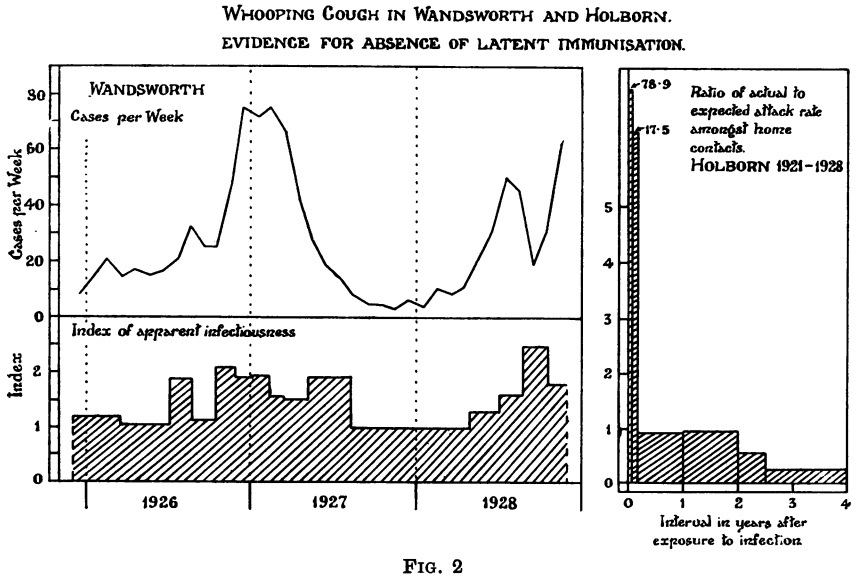

FIG. 2

During the first half of 1926 incidence was low, with about fourteen cases per week; from July 13 to August 23 it rose to thirty-three per week, fell again to twenty for the next eight weeks, and then followed an epidemic which lasted until the end of April with sixty to ninety cases per week occurring from November to March. Incidence was at a low level for fourteen months from May, 1927, to June, 1928, rose to about fifty per week during July and August, fell again temporarily during September, and reached epidemic proportions again at the end of the year.

For the purpose of calculating the index of apparent infectiousness, a secondary case was defined as a case under 15 years of age who began to develop whooping-cough four to twenty-eight days after another case of any age in the same house. Onset in whooping-cough is not of course very easy to date exactly, and the records in many cases only placed it to the nearest week, giving an irregular distribution of intervals, which has been smoothed in Table I.

It is evident from fig. 2 that the apparent infectiousness rose at the start of the 1926 epidemic to about double its pre-epidemic level, and remained high until the end of July, 1927, some two or three months after the epidemic had subsided. It then remained low for nine months and rapidly rose again to two and a half times its normal level before the autumn epidemic in 1928. During the unit period from August 9, 1927, to April 30, 1928, there were 266 cases, followed by 36 secondary cases as defined, a ratio of 13·6 per cent., whilst during the six weeks October 19 to November 29, 1926, there were 235 cases followed by 69 secondary cases, a ratio of 29·4 per cent., giving an index of 2·16 for this period. The sudden fluctuations shown in the diagram can safely be regarded as statistically significant and not due to sampling errors; thus in the six weeks July 13 to August 23, 1926, the percentage of secondary cases was 24·4 ± 2·0, in the sixteen weeks preceding it was 14·8 ± 1·6, and in the eight weeks following, 16·0 ± 1·9. These sudden fluctuations can scarcely be due to changes in communal immunity and must therefore presumably be due to changes in facility of transmission.

The absence of any gradual fall in the index during the progress of the epidemic, or of any pronounced difference between the indices before and after the epidemic suggests that latent immunization must be absent or at least not a factor of importance. This has been further tested from the Holborn notification records. Every child under ten who was a contact in the same house as a case of whooping-cough during the seven years from mid 1921 to mid 1928, and who had not had the disease, was followed up through the records and the date of any subsequent attack noted, and the interval since exposure as a contact. The age distributions of the total children at risk after the lapse of 6 months, 1 year, 1½ years, and so on, from the time of exposure were worked out and the expected attacks during intervals 0-½ year, ½-1 year, 1-1½ years . . . were calculated from these by multiplying the number at each age by the mean attack-rate per 1,000 susceptibles in the population at that age and making a correction for removals during the interval. The mean attack rates used for standardizing were obtained from the yearly births, deducting deaths and notified cases and thus arriving at the mean population of susceptibles at each age, giving, when divided into the notified cases, the following rates per thousand susceptibles during the septennium :—

Age	0	1	2	3	4	5	6	7	8	9
Rate per 1000	30·6	34·4	38·9	46·6	40·6	39·5	30·1	11·8	3·1	3·2

Thus there were 697 children under ten at risk over at least 1½ years, and the expected attacks on the basis of their age distributions and the above rates were 21·96 during a whole year or 10·98 during the half-year period 6-12 months after exposure, or after deducting the number likely to have removed after that time as calculated from the annual deductions from electoral registers, the expected attacks notified became 8·86. Proceeding on this basis for successive intervals after

TABLE II.—SUBSEQUENT BEHAVIOUR OF 721 CHILDREN UNDER 10 YEARS OF AGE WHO WERE CONTACTS TO WHOOPING-COUGH IN HOLBORN DURING 1921-28.

Time after exposure	Expected attacks	Actual attacks	Ratio of actual to expected
4-28 days	1·88	153	81·4
1-2 months	1·94	34	17·5
2-3 ,,	1·94	2	
3-6 ,,	5·82	7	0·93
6-12 ,,	8·86	6	
1-1½ years	7·75	7	
1½-2 ,,	5·80	6	0·96
2-2½ ,,	5·13	3	0·58
2½-3 ,,	3·61	0	
3-3½ ,,	2·96	0	
3½-4 ,,	1·91	1	
4-4½ ,,	1·46	1	0·26
4½-5 ,,	0·85	1	
5-5½ ,,	0·55	0	

exposure to infection the observed and expected attacks and the ratio between them were as shown in Table II. The ratios are also shown diagrammatically in fig. 2, and it is clear that, after the immediate risk of infection had subsided, the contacts were subject during the first and second year to almost exactly the expected rates and there is therefore no evidence of any acquired protection through exposure. The falling rates after two years, even if statistically significant, which they are not, could not be due to latent immunity.

The conclusion is that there is here twofold evidence against the existence of latent immunization to whooping-cough being acquired by close contact, but, nevertheless, in spite of little isolation of cases being practised at home and the length of the infectious period, it appears that out of 721 contacts under ten who had never had whooping-cough only 187 contracted the disease within two months and 221 within four years[9] of exposure. This suggests that about 70% of contacts under ten years of age who have not had whooping-cough will escape it altogether. In Wandsworth, the average cases per year from 1926-28 were 1,401, whilst the population of children was being replenished at the mean annual rate of 4,527 survivors of the first year, so it would appear that about 70 per cent. of all children born are likely to escape the disease. From the age distribution of cases it follows that about 80 per cent. of all children under ten who have not yet had the disease in the population will escape it altogether, as compared with about 70 per cent. of those who were contacts. It must therefore be concluded that the bulk of children escape whooping-cough by virtue of an inherent immunity rather than by avoiding contact with infection.

Chickenpox.—Chickenpox offers in this country an almost virgin soil to the statistician, apart from some hospital statistics, but fortunately it has been notifiable in Paddington for a number of years, and thanks to the Medical Officer of Health, Dr. G. E. Oates, I have been able to work out the index of apparent infectiousness over five years from 1925-29. Fig. 3 shows the mean weekly case incidence in each month during the seven years 1923-29, and the resulting curve presents some interesting features. In each of the seven years there was a peak either in June or July, and the heights of these successive summer peaks form such a beautiful series that I could not resist the temptation to draw a spline curve through them as shown by the dotted line. Whether or not the periodicity of about six years which this suggests is a real one and not merely accidental, I cannot say with confidence, and I am afraid all we can do is to wait and see.[10] The peak month was June in 1924, 1925, 1926, whilst the annual incidence was increasing, and July whilst it was decreasing. There was also in each year, except 1929, a second peak in October or November, and one might also draw a curve through the tops of these which would be roughly inverse of the other, that is to say a small summer peak was usually followed by a considerable autumn peak. The annual totals of cases from 1923 onwards were successively 753, 718, 852, 1,123, 788, 924, 558.

The distribution of intervals between cases which occurred in the same house is shown in Table I, and a secondary case for the purpose of the index of apparent infectiousness was defined as a child under 15 who developed the rash twelve to sixteen days after a previous case in the same house. The changes in the index during 1925-29 are shown in fig. 3, and it may first be noticed that every one of the nine epidemic periods, whether summer or autumn, was preceded by a sudden increase in apparent infectiousness to three or four times its ordinary level. To prove that these fluctuations are statistically significant we may take, for example, the first one, in 1925: thus, from January 1 to April 4 there were 160 cases, followed by twenty-five secondary cases, a percentage ratio of $15 \cdot 6 \pm 1 \cdot 9$, and from

9 The mean period at risk of the 721 cases was 4·1 years.

10 It is interesting to notice that the annual totals of reported cases in Chicago from 1911 to 1926 [19] show minimal levels in 1912, 1918 and 1925, and maxima at 1917 and 1924.

April 5 to May 2 there were sixty-five cases, followed by twenty-four, a percentage of 36·9 ± 40, the difference being 21·3 ± 4·5. These sudden fluctuations must be due to changes in true infectiousness.

In 1926, when the highest summer peak was reached, the sudden access of apparent infectiousness occurred in March; in 1925 and 1927, when a moderate summer peak was reached, the rise in index did not occur until April, and in 1928 and 1929, when there were only very small summer peaks indeed, it was delayed till May or June. Evidently infectiousness must rise early in the spring in order to produce a large summer epidemic. An invariable feature of the incidence curve is a low rate in September, and it might seem that an obvious explanation of the break between the summer and autumn maxima is the summer holiday, which stops the spread of infection in schools, and that apart from this they would be fused into one. I think the behaviour of the index proves that this is not the real explanation. The index cannot be appreciably affected by school closure, for the

CHANGES IN APPARENT INFECTIOUSNESS OF GERMAN MEASLES AND CHICKEN POX. 1923–1929.

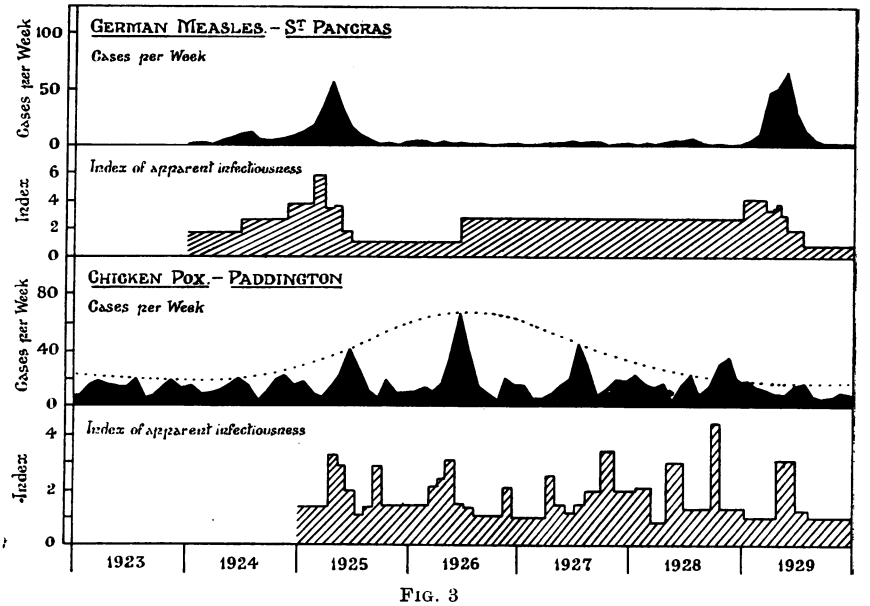

FIG. 3

spread of infection which it measures is between children living together in the same house, and since contacts are excluded from school, the children will be as much together at home whether schools are closed or not. It appears from the data that in every year the infectiousness gradually or rapidly subsided from a high to a low level *early* in July, and did not rise again to a high level until October or November, proving, I think, that the low incidence in August and September was the result of seasonal factors unconnected with school closure.

If we seek to relate the rise and fall of the index from one steady period to another, with the depletion of susceptibles occurring during the interval, then, measuring the index at the middle of steady periods of low incidence, we find that from January, 1925, to February, 1926, the index rose from 1·39 to 1·42, with 988 cases; from February, 1926, to March, 1927, it fell to 1·03, with 1,153 cases; from March, 1927, to April, 1928, it fell further to 0·78, with 1,064 cases; and from April,

1928, to March, 1929, it rose again to 1·01, with 822 cases during the interval; thus :—

No. of cases ...	822	988	1,064	1,153
Change in index ...	+·23	+·03	−·25	−·39
Interval in months ...	13	13	13	11

This suggests that the apparent infectiousness was maintained at a constant level (apart from seasonal fluctuations) when cases were occurring at the rate of about 950 to 1,000 in thirteen months, or 900 per annum. The annual births in Paddington during 1922-28 added fresh children to the population at an average rate of 2,223 survivors of the first year of life per annum, so it appears that to every two notified cases there are three children who either have inherent immunity or have chickenpox unnoticed or unnotified, or acquire latent immunity to it.

In order to ascertain whether latent immunization does occur, a method is now being applied which has been made possible through the courtesy of the Health and Education departments of the London County Council, but I have not yet been able to follow up enough contacts to answer the question with certainty. I give the preliminary figures, postponing any elaborate analysis until much larger data have been collected for this and the other diseases. By following up through the records of the various departments 151 children, aged 5 to 7, who were excluded from eight Paddington schools during 1926-28 as contacts to chickenpox cases at home, it was found that twenty-seven developed the disease within three months, or about 18 per cent., leaving 124 at risk at the end of three months. These were followed further through the records over varying periods up to three years, during which none passed the ninth year of age. The aggregate number of years at risk was 219 and four cases of chickenpox occurred, or 1·8 cases per 100 years at risk. The control group, selected in exactly the same way at the same ages [11], in the same years and at the same schools, except that they were excluded as contacts to some disease other than chickenpox, consisted of 296 of whom three contracted chickenpox soon after exclusion, leaving 293 at risk after the lapse of three months. These were then exposed to risk over an aggregate of 461 years, and twenty-three cases of chicken pox occurred or 5·0 cases per 100 years at risk. The probable errors of these rates are of the order of ·7 and ·8 respectively, so the difference between 1·8 and 5·0 may be regarded as statistically significant. The rate of five cases per 100 years at risk implies a mean annual attack-rate at ages 6, 7 and 8 combined [12] of about 5 per cent., and this may be compared with the mean attack-rates per 100 in the whole population of Paddington at these ages during 1925-28, which were approximately 7·1, 4·4 and 2·5 respectively, or a mean rate of 4·7.

The lower attack-rate of 1·8 per cent. in the children who had been exposed to infection but escaped, might conceivably be due to either (1) selection by the disease of the most susceptible, leaving a residue less susceptible on the average than the controls, or (2) latent immunization of those exposed.

As regards selection the facts might be explained if we suppose that about half the children born have an inherent immunity to chickenpox and escape the disease for that reason.[13] Another quarter will have chickenpox by 6 years of age [14], leaving about a quarter of any random sample about that age susceptible. On this basis of 100 contacts about this age eighteen catch the disease within three months, leaving eighty-two at risk, of whom only seven are susceptible, whereas of 100 controls only one catches it within three months, leaving ninety-nine at risk, of

11 The mean age of the control group was 5·88, and of the contacts 5·75 years, the percentages aged 5 being 36·6 and 37·8 respectively.

12 The 5-year-olds at time of exclusion would average 5½ years, and after allowing 3 months to elapse, 5¾ years, before they were at risk.

13 The histories analysed by Collins show that 52% reach the age of 17 without having chickenpox in American towns, and the Paddington data suggest a similar figure.

14 The Paddington data for 1925-28 show that of 3,696 cases 2,027 occurred before age 6.

whom twenty-four are susceptible, so that the subsequent attack-rates, given equal chances of infection, should be as 7/82 to 24/99, or as 1·8 to 5, which is the ratio actually found.

On the other hand these facts could be equally well explained by latent immunization with about one latent case to each clinical case, and to settle which of these is the correct explanation or whether both play a part, further data are necessary. I have worked out the attack-rates up to the end of 1928 amongst 3,416 contacts at different ages up to 10 in the whole of Paddington during 1925-28, and the results are shown in Table III. After the first year, when there is as usual evidence of some congenital immunity, there is a steady fall in attack-rate among

TABLE III.—FATE OF CONTACTS TO CHICKENPOX IN PADDINGTON, 1925-28.

Age	Total	Per cent. of contacts who had not previously had chickenpox	Per cent. of these who contracted it up to the end of 1928
Under 1 year	215	99·5	43·0
1-2	515	98·6	58·6
3	373	92·0	55·1
4-5	693	75·7	50·5
6-7	687	62·4	42·2
8	316	47·8	36·4
9-10	617	41·5	30·9

contacts from about 60 per cent. in the second year of life to about 30 per cent. in the tenth year, and this suggests that there is a process of latent immunization of a fairly permanent character in progress, for if there is only an inherent immunity the rate should not vary much with age. The combined evidence so far as it goes suggests that a certain proportion, possibly about a quarter to a third, of children born retain an inherent immunity, and that latent immunization protects others, possibly another quarter, but if this is so the ratio x of latent to clinical cases must be low, perhaps one to every two cases. Further research on these lines will doubtless settle these points.

Measles.—As early as 1913 Butler [12], in a very interesting paper to this Section, suggested the possibility of latent immunization in measles, whilst Halliday [20] in his admirable report on measles in Glasgow tenements, published a few months before my first paper on measles was in the press, actually made the suggestion that there might be a latent immunization of a temporary character. I confess that whilst I had read both these papers I had overlooked the sentences in which these suggestions were made. In a second paper on measles recently published in the *Lancet* [21], a graphic comparison of the St. Pancras data with the Willesden data of Butler has been made, and I have also carried the analysis of a measles epidemic a stage further and produced some additional evidence for a temporary latent immunization of the child population during an epidemic. Only brief reference need be made here to measles, and I have reproduced fig. 4 in order to show how the behaviour of the index of apparent infectiousness compares with its behaviour in the other diseases. The distinctive feature is of course the fairly rapid rise of index between one epidemic and the next, which has been shown to be far too rapid to be accounted for by the mere accession of fresh children at risk to the population. On this is superimposed the usual sudden increase in true infectiousness which appears to remain enhanced throughout the epidemic when a large area is being dealt with as here, but when analysis is made into smaller districts about half a mile square, it is found that as the epidemic travels slowly from one square to another, it is always preceded by a sudden access of infectiousness to about ten to fifteen times its post-epidemic level, which then steadily subsides in about six weeks, and thus the composite picture makes it seem that the infectiousness is at a high level throughout.

When the progress of the epidemic was thus followed over the map it was found to follow streams of flow depending upon barriers to free communication produced by extensive railway depôts and it appeared that the index of infectiousness rose and the epidemic started, for example, some twelve weeks later in Chalk Farm area than in Tufnell Park a mile away. These facts may later throw an interesting light upon the puzzling results which Brownlee obtained from periodogram analysis, but they seem at the moment to prove that the explanation which he gave of those results cannot be a correct one. They also show that in producing the sudden access of true infectiousness which precedes the epidemic wave wherever it travels, atmospheric influences must be of secondary importance, and the probable explanation is on the lines of Gill's quantum theory, that when the balance between the number of cases or carriers and atmospheric conditions on the one hand, and the density, freedom of circulation in schools and streets and average immunization of the

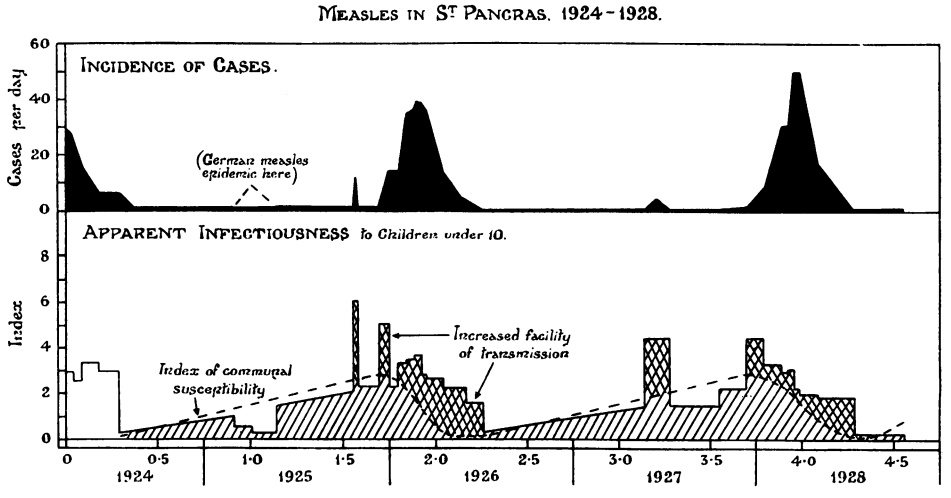

Fig. 4.

population on the other, passes a critical point, transmission of the virus is stimulated, and the epidemic goes forward till all the children who are not specially sheltered have been either permanently or temporarily immunized.

In fig. 5 I have shown what must happen to the child population in an urban area when subjected to a measles epidemic on the assumptions, all supported by a certain amount of evidence: (i) that an epidemic occurs every two years, with three-quarters of the biennial total of cases occurring in the epidemic six months and one-quarter in the eighteen months between; (ii) that children fell victims to measles in successive two-year periods at the rates obtained by Collins [13]; (iii) that latent immunes are produced at a rate of three to each case; and (iv) that latent immunity is lost at the rate of 50 per cent. in one year and 100 per cent. in two years. It appears that on this basis almost complete immunization of the mobile portion of the child population (aged three and upwards) will be brought about before the epidemic ends, leaving only very young children unprotected, doubtless those not in families with older children and who have therefore avoided contact with sources of infection.

A fuller explanation of this analysis and that of the progress of an epidemic in space is to be found in the paper referred to [21].

German measles.—In St. Pancras German measles is a notifiable disease, and during the six years 1914-29 there were 2,484 cases, of which 1,940 occurred in the two epidemic years 1925 and 1929. In the long periods between epidemics the incidence was at the rate of one to five cases per week, and, at the height of an epidemic, sixty to seventy per week. The distribution of intervals between successive cases in the same house, during 1924-28, is shown in Table I, and the most suitable range of intervals for the purpose of defining a secondary case seemed to be six to twenty-two days. The incubation period is more variable than in measles, and smaller intervals of days than six were probably for the most part due to infection from a common source, and cases occurring after such short intervals may be termed associated primary cases. It makes little difference whether the index be calculated on the basis of the secondary cases alone, or whether the associated primary cases are also included, since both tend to rise or fall with infectiousness; hence the numbers being somewhat small for this disease, the index was calculated on the basis of any interval up to twenty-two days, the second case being a child under 15, and the date of onset being the date of appearance of the rash.

IMMUNITY CHANGES IN THE CHILD POPULATION OF AN URBAN AREA DURING A MEASLES EPIDEMIC ON THE THEORY OF TEMPORARY LATENT IMMUNISATION.

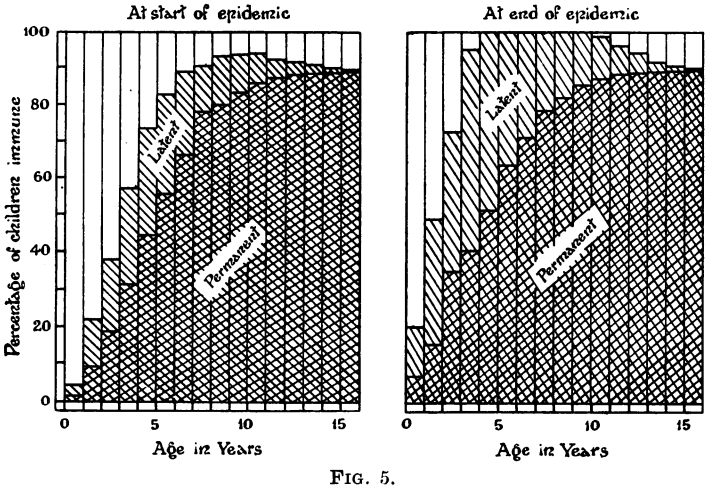

FIG. 5.

The behaviour of the index throughout the six years and the curve of cases per week are shown in fig. 3, and we again find the gradual rise in apparent infectiousness between one epidemic and the next, the sudden increase just preceding the epidemic, and the rapid fall to a low level whilst the epidemic is in progress. The rate at which the index rose between the epidemics averaged a 2·8-fold increase in one and three-quarter years, from January, 1926, to October, 1927, and from this we may conclude that the susceptible children under 15 doubled in numbers in a little over a year. During this period cases of all ages were being notified at the rate of 111 per year, and the population replenished at the annual rate of 3,225 survivors of the first year of life, so that about 3,100 were being added per annum to the population at risk, or between one epidemic and the next about 12,000. Since each epidemic consisted of only about 800 notified cases, we must either assume that there is widespread inherent immunity to German measles, or else that latent immunization is an important factor, as in measles, and which of these is the correct explanation can only be settled by further research.

In conclusion, I should like to urge that everything possible should be done to make our notification records as accurate as possible, for important advances in our knowledge of the mechanism of epidemics can undoubtedly be made from a study of them, and that local authorities may be requested not to destroy their notification forms as is now the usual practice after three years, thus rendering research of this kind almost impossible, but to keep such records, so that in future years they may be available for research. On this latter point I speak with feeling, for owing to the destruction of records it will now be necessary to wait five or ten years to settle some simple and fundamental points which could have been settled now if they had been kept. And finally, I would urge that a few more local authorities may use their powers to introduce compulsory notification of such diseases as chicken-pox, whooping-cough, measles, and influenza, in order to make statistical research possible.

I wish here to record my indebtedness to my assistant, Miss M. N. Karn, for her help in collecting and analysing the data, to Miss I. MacLearn, for drawing the diagrams, and to the Health Departments of Paddington, Holborn, Wandsworth, St. Pancras, and the London County Council, for their assistance.

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Discussion.—Sir WILLIAM HAMER: Forty years ago experiences recorded by W. H. Power at Brailes and Pirbright compelled school doctors to realize the importance of the "missed case." This lesson was forced upon my attention by an outbreak of diphtheria at Lewisham Bridge School in 1896, and, here in this room seventeen years later, a paper was read, in which it was stated that I must have suspected the existence of "bacteriological carriers," "missed" and "unrecognized" cases, for I "had referred to such cases under the generic name of throat illness." I blushed, needless to say, on hearing my true character thus revealed, as originator of the "healthy bacillus-carrier" hypothesis, but felt some doubt and misgiving on the subject, inasmuch as one of the main points stressed in my report was the discovery of a number of "mild *cases of illness*, the nature of which had not been recognized." My rough guess, in the Milroy Lectures of 1906, was that London measles-susceptibles ranged (at that time) between 180,000 and 120,000, and this guess tallies fairly well with Mr. Soper's recent and precise statistical analysis for London as a whole. Of course, studies made in Plumstead by Dr. C. J. Thomas and Dr. Sidney Davies, a quarter of a century ago, would yield a very different range, did we but (to quote Sir Thomas Browne's phrase) "difference nearer and draw into a lesser circle" of the infants' departments of the elementary schools of poor neighbourhoods: for Dr. Thomas writes that "the second crop exhausts practically all the susceptible cases." Moreover, one London prevalence may be particularly severe in the south-east, another in the East End, and so forth; and thus the Plumstead experiences of Dr. Thomas and Dr. Davies stand shoulder to shoulder with those of Dr. Percy Stocks in Chalk Farm and Tufnell Park. With such facts in mind, the number of susceptibles in infants' departments of hard-hit poorer quarters of London might well show reduction, during a measles outbreak, from, say 25,000 to 5,000, a range quite wide enough to justify the conclusion that "rise and fall in the proportion of

children protected by previous attack of measles" in such infants' departments, might well "be regarded as the chief cause of periodicity." As showing that, even nowadays, many cases of measles are "missed," or "unrecognized," I prepared a table (*Ann. Rep.*, 1913, Diagram H, opposite p. 199) which reveals the fact that a quite noticeable modification of the graph representing school notifications of measles is that produced during the period immediately after Easter, when "scheduling" is in progress. The depression is "not so deep as a well nor so wide as a church door," but "'twill serve" to prove how marked an influence is exerted upon notification statistics by any relaxation in the extent to which "following-up" inquiries regarding absentees from school are being pressed. Such considerations as these may be mentioned as supporting the recommendation (made by Dr. Stocks) that "everything possible should be done to render our notification statistics as accurate as possible."

Professor M. GREENWOOD: The researches upon which Dr. Stocks is engaged, part of which has just been described, seem to me among the most important contributions to epidemiological science now being made. Dr. Stocks, like Professor Topley and myself, is not proposing for himself so noble a quarry as Sir William Hamer and Dr. Crookshank, or the late Dr. Brownlee had, if not in view, at least in mind, viz., a general doctrine of epidemicity. He is seeking to describe accurately the particular phenomena of particular illnesses, using what I may call a general demographic method. In his work the "exposed to risk"—as an actuary would call them—are made up of smaller groups—e.g., family groups of different sizes and under different environmental conditions—for each of which the conditions are, perhaps, different, and he is seeking measures of the *average* effects. This is a fundamentally important line of approach, and Dr. Stocks deserves great credit for perceiving that notification data afford material and for *acting* upon that perception. I do not quite share his belief that a general extension of the system of compulsory notification, either geographically or with respect to other diseases, would be helpful. One or two areas, the public health officers *and* the clinicians of which have been convinced of the interest of the work and have agreed on criteria of notification, will provide far better data than ten times as many districts in which a system has been adopted which they regard with indifference, or even dislike.

This general demographic method is also used by Professor Topley and myself in our studies of mouse-villages, and in some respects our results run parallel with those of Dr. Stocks, as do our difficulties of interpretation. We, for instance, are satisfied that acquired immunity, an immunity which is certainly far from absolute and probably transitory, is an important factor and we too have experienced Dr. Stocks' difficulty in assessing the respective shares of such acquired immunity and of natural resistance.

Side by side of these general demographic studies, intensive studies are being made; Surgeon Commander Dudley's work is an important example. He is able to watch the happenings in a small community, the vital statistics of which he knows accurately. Similar, but of course less exact, work is being done in various public schools under the general guidance of a research committee appointed by the Medical Research Council.

I have also been interested for many years in the analysis of the distribution of multiple cases in houses containing different numbers of exposed to risk. During the War, Mr. Udny Yule and I were led to study a cognate problem, viz., the frequency distribution of accidents sustained by factory workers. We wished to discover whether the form of frequency distribution—number of exposed who had had no accident, number who had had one accident, number who had had two accidents, etc.—would enable us to form some judgment as to ætiology, i.e., whether accidents were really "chance" events, whether sustaining one accident made the victim more (or less) susceptible to a second accident, etc. We obtained and published ten years ago a first approximation to the solution of this problem. The problem of cases of disease is somewhat different, thus, while there is no theoretical limit to the number of accidents an individual might sustain when the period of observation is long, there cannot be more than n "cases" of disease in a household of n members. There is, however, close similarity between the statistical methods applicable. Sufficient work has already been done to make it certain that the distribution of multiple cases of such a disease as measles is neither random, in the statistical sense of the word, nor does it approximate to the opposite extreme, viz., that when there are n exposed to risk, the frequency will collapse into the mere discovery that all of the n will take the disease. Before we can usefully devise a mathematical schema, we must set our scientific imaginations to work and speculate about what really happens in a community wherein n susceptibles are exposed to, say, one infective

person. Is there a process of bombardments, does one "hit" in each of successive time intervals lead to a different clinical result from two "hits" in the same interval, etc.? A very little reflection shows how difficult and how fascinating this sort of investigation is and also that frequent cross-references between the demographic and the intensive researches are imperative.

Surgeon Captain S. F. DUDLEY said that one difficulty alleged by some workers in accepting any latent immunization hypothesis was that carriers were not sufficiently ubiquitous. He thought this objection was due to a failure to realize that if the duration of infection was short, a large proportion of the community could become infected, although at any instant of time the carrier-rate was small. That this was true he had proved directly in the case of diphtheria by swabbing a random sample of 139 normal schoolboys eight times in the course of one year. Fifty-five, or 40%, of this sample were found to carry Klebs-Loeffler bacillus (about half toxigenic) on one or more occasions during the year, but only 9% were infective at more than one of the eight swabbings. The percentage of total swabs infected was 6; about the same carrier rate as in the L.C.C. schools. If the same set of conditions continued over the ten years of school life, there would be enough different latent infections for every school child to be a carrier four times. He was glad Dr. Stocks was giving attention to the "circulation factor" or the effect of the amount and type of motion of individuals within, without, and to and from the herd. It was a factor that must be vary variable at different times and places, yet it must be of great importance but presenting very great difficulties in measurement. Finally, as an amateur biologist, he was loth to give up his belief that some kind of adaptive variations in the characters of infecting agents, such as parasitic "herd virulence," was not just as essential a cog in the mechanism of herd-infections as herd-immunity.

Dr. J. D. ROLLESTON, after alluding to the "formes frustes" of scarlet fever described by Trousseau, and the "febris morbillosa" of Sydenham, as examples of incomplete forms of infectious disease in the pre-bacteriological era, said that the staff of a fever hospital offered an excellent opportunity for the study of latent spontaneous immunization. Infectious diseases were most likely to attack the young nurses or medical officers who had recently joined the staff, but, occasionally, as Zoeller[1] had shown, the action of spontaneous immunization was capricious, and persons who for many years had been in contact with infectious cases suddenly contracted diphtheria or some other acute disease to which it might have been supposed they had become permanently immune. According to Zoeller, no less than 36 per cent. of the medical staff in departments for infectious disease showed a positive Schick reaction and therefore required active immunization.

Dr. STOCKS (in reply) said that the possibility of variation in the normal level of virulence of the infecting agent owing to "biological modification" must not of course be lost sight of, but if we were to arrive anywhere in research of this kind we must assume some factors to be constant. A step forward had been made in attempting to take into account the simultaneous variation of two factors instead of one only, and at present it was necessary to suppose that the same strain of virus persisted in a district over the short period of years under review. In regard to Sir William Hamer's difficulty as to how a ratio of, say, three latent cases to one clinical case in measles, fitted in with the fact that in an infants' department of a school heavily attacked by an epidemic, almost every child at risk sometimes took the disease—this was doubtless a question of intensity of infection. If a large number of cases or carriers happened to occur together in a school, the velocity of infection would be such that most children at risk would succumb to a clinical attack, and the ratio in that school would be less than three to one, whereas if cases occurred at intervals, so that smaller doses of infection had to be dealt with in a given time, many of the children would acquire latent immunity rather than a clinical attack and the ratio would be greater than three to one. The ratio calculated in St. Pancras must be regarded as an average ratio over the whole district.

1 *Bull. et Mém. Soc. méd. Hôp. de Paris*, 1928, lii, 426