CHAPTER VI.

NATURAL IMMUNITY.

It is important for both general and particular reasons to know whether passing through an attack of influenza renders the victim less liable to be again successfully attacked. The general reason is that if a large proportion of the victims is rendered immune from second attacks then, where the disease has been widely prevalent, it should follow that an appreciable proportion of the inhabitants might become insusceptible, a proportion sufficiently large to diminish the chance of another outbreak attaining considerable dimensions. The particular reason is that successful natural immunisation would guide us in attempts to confer an artificial immunity by inoculation.

Owing to the importance of the matter, efforts were made to secure data over a wide field. The kind of material desired was samples of persons living under various conditions of whom the influenzal records through two or three periods were accurate, *i.e.,* we desired to know how many of the group were attacked in the summer and how many not how many of each of these classes were attacked in the autumn and similar information respecting the third wave.

That the effect of differences in environment and geographical situation might be noted, sample censuses were made in several cities and inquiries were also directed to some boarding schools. Data relating to members of the University of Cambridge, and to a police force were also secured. The original material so far as relevant to the present inquiry is recorded in Table I. (further particulars of certain data are given in the appendices). The appraisement of these results is a matter of considerable difficulty and it will therefore be proper to discuss in detail the methods employed.

All statistical inquiries involve two orders of difficulty, material and analytical. The material difficulties are those due to imperfections of the crude data themselves. Such imperfections, or errors, are of two kinds, systematic and unsystematic. Systematic errors are introduced in two ways. The first, and less important, is deliberate or unconscious bias of recorders. Thus a recorder who believed *a priori* that an attack of influenza did confer immunity, might accept evidence that a person who was not attacked in the autumn had been attacked in the summer with less criticism

than he would apply in other cases. This source of systematic error (another form of which is to reject observations making against a theory with greater readiness than those making in its favour) has, we think, not occurred in our series. A more prominent source of systematic error is introduced by the method of sampling used. If a house to house visitation be the source of the statistics it may be easier to obtain information from particular types of household and it was actually found that this happened. Families containing young children are proportionally over-represented in the censuses because tenements occupied exclusively by adults were more likely to be empty at the times of day when the particulars were collected. Hence the samples are not random samples of all households, but only of households of a particular class. The effect of this upon our investigation is not, however, of serious importance.

In the school inquiries it is possible that some systematic error may have been introduced by a failure to record accurately the changes of the population *i.e., we* have an insufficient guarantee that all *said* to be exposed to risk throughout the period of observation were really so exposed and that no others were exposed. It was obviously not possible to subject such data to the rigid control practicable when the whole investigation was guided by the staff of the Ministry or by experienced medical officers of health. There is, however, no reason to believe that any important error of this kind has occurred. Upon the whole it is felt that the prejudicial effect of systematic error has been sufficiently slight to disregard. Unsystematic errors are those due to carelessness or random inaccuracy on the part of the recorders or to inherent difficulties in making exact specifications. These have indubitably entered largely into the matter. Many of the particulars have been gathered by untrained or partly trained observers working often under pressure, while, even for the expert clinician or epidemiologist, to decide upon the evidence of an uneducated witness whether he or a member of his family had had an attack of " influenza " is a matter of delicacy. Hence we do not suppose that a high standard of accuracy has been reached.

There is, however, an important difference between the statistical consequences of systematic and unsystematic errors of record. The former might lead to a totally false conclusion : the latter would in general merely blur the analytical results, although they might lead to a negative conclusion where good data would warrant a positive conclusion. In some inquiries, notably those of psychologists, allowance is made for the attenuation of the statistical results due to such unsystematic errors. We shall not, however, attempt any such refinements here, since, for reasons about to be discussed, the range of fluctuation in results deduced from perfectly accurate data of the present class is so great that it is unprofitable to pause upon minutiæ.

We now turn to the analysis of the data and the expression of their meaning in the form of statistical averages. From the outset, two points are obvious. One is that if a first attack of influenza does confer any protection, then the case rate of those previously attacked will be less than that of those not before attacked. The other point is that variations of case rate might and do occur quite irrespective of previous history.

We can display the principle with the help of a time honoured illustration. If we draw counters at random out of a bag containing equal number of white and red counters, we shall rarely draw precisely equal numbers of each kind. If in a series of trials, or in a single trial, there is a clear majority of red counters, we shall not infer that it is really easier mechanically to extract the reds, unless we can show that the discrepancy is much greater than would be likely to arise by mere chance in the extraction of samples of the given size from a bag containing perfectly similar and equally accessible red and white counters. The arithmetical criterion applicable to such a case is simple. If the proportion of red counters is *p,* and of white counters $1 - p - q$, then if *n* are drawn (it is assumed that either the total number in the bag is indefinitely great or that each counter is replaced after drawing) we shall *on the average* draw *np* red counters per sample of *n,* and the chances are that a considerable majority of the drawings will not differ from this average by more than two or three times *npq.* Why then should we not apply this method to the. case of influenza? If a previous attack confers no immunity, the *n* persons attacked in the summer, and the *m* persons not attacked in the summer may be likened to samples drawn from a bag, which bag is to be composed of red and white counters in the proportions representing the total attacked and total not attacked *during the autumn,* and, if there be no immunity, the difference between the proportions of attacked in the two samples should not greatly surpass the expected fluctuation determined by the formula quoted above.

There are two objections to this process. The first, and more important, is that the formula measuring the extent of fluctuations is deduced on the assumption that the drawings are independent, that if the first counter drawn in any trial happens to be red it is neither more nor less likely that the second will be red than if the first had been white. Suppose the bag of counters subject to other conditions. That, for instance, the colours in the bag were changing, sometimes white counters turning red, sometimes red counters turning white. Suppose that the mere drawing of a counter and its replacement made a difference, that when a white counter was drawn and thrown back into the bag, any red counter it impinged upon turned white. Clearly the law of fluctuations in sampling such a bag as this might be very unlike those of

the time honoured and static "universe" of counters which provides our simple formula. But a moment's thought shows that the statistical nightmare we have just conjured up is more nearly in point when we are discussing an infectious disease than the orthodox scheme. The chance of contracting an infectious disease is ill represented by taking the proportion of those affected by the disease in the " universe," and using that proportion as the constant measure of risk for each person. The " counters " are *not* all alike in shape and smoothness, and the drawings are *not* independent. These two departures from the scheme will affect the variations of the composition of samples in different ways, but, in the general case, the combined bias will deprive the formula of much practical value. In fact, a very good statistical criterion of infectivity is to note that the fluctuations of samples, *e.g.,* the numbers of houses with 0, 1, 2, &c. cases of diseases in different samples *are* quite unlike those which would occur upon the hypothesis from which we started.

Are we, then, to conclude that arithmetical computations based on the theory of simple sampling are mere waste of time in the present connection ? The answer is that such calculations although of very limited value, are not entirely worthless. The present differs materially from such a statistical record as, for instance, the number of cases of infectious disease in each of a series of years or the distribution of cases in houses. In either of these the method is valueless. It would be useless to use it to measure the probability that the attack rate in Manchester (measured on a sample of the inhabitants of Manchester) differed significantly from a sample in Leicester. But the data we are to analyse consists, in each sample, of persons under a common environment all exposed to a considerable average risk of infection. Those previously attacked were not segregated in any way from those not previously attacked, while the evidence we have analysed in another chapter makes it a matter of doubt whether variations of domestic conditions (which in any event do not apply to the schools) are very compelling factors. Hence it may well appear that the time-honoured test is not altogether useless, but may at least serve to indicate a lower margin of fluctuation, so that deviations found by it to be within the limits of chance fluctuations may certainly be dismissed as insignificant. It may still be objected that there is another difficulty; even were the counter drawing analogy tolerable, we do not actually know the contents of the bag. We know the numbers attacked by influenza *in our samples* not in the universe of which they *are* samples. This objection is, however, much less formidable than the former because the combined totals of the samples are large and if the analogy were valid, the risk of assuming the proportion obtained in the combined samples to be that of the whole universe does not import any great error into our calculations.

If we are to use this method as a preliminary test, the question next arises as to whether we can render our results comparable by the eye, if we use some function of the proportions instead of the proportions themselves, since the latter will vary with the severity of the epidemic in the particular town or community studied. A method which suggests itself is to compare 100 (p1-p2)/p1 for the different samples where p1 is the proportion attacked in the second epidemic of those not attacked before, and p_2 is the proportion attacked amongst those who had been attacked before. This expression, which has been termed the percentage efficiency of protection, has the merit of varying from 0 to 100, when p1 is equal to or greater than p_2, but it has various demerits. For instance if p1 is less than p_2 the range of negative efficiencies is unlimited and to reach a correct mean value needs a series of comparisons strictly *in pari materia**

Consequently this method of comparison is not very good. Actually we provide the following statistical deductions based on the method of simple sampling.

(1) The number attacked in the second of each pair of epidemics from amongst the previously attacked, and the ratio of the difference between this and the "expected" number to the latter's probable error on the assumption of independent liability, the chance of attack being defined by the ratio of attacks to persons at risk in the combined second samples.

(2) A comparison of percentage attack rates.

(3) Percentage efficiencies, together with the probable fluctuation of such a measure around the value zero which would be almost its mean value in an undifferentiated population (the probable fluctuation has been calculated on the hypothesis of independent chances).†

This method being admittedly imperfect although easy to grasp we turn to others. The most usual is to tabulate the data in such a form as the following:—

1st Epidemic.	2nd Epidemic	
	Attacked.	Not Attacked.
Attacked - -	a	b
Not attacked -	c	d

* For a full discussion of this and other points, touched on in the text, *see* Greenwood and Yule, Proc. Royal Soc. Med. (Section of Epidemiology and State Medicine) VIII, 1915, pp. 113-190.

† *I.e.*, if *p* were the proportion attacked in the second epidemic, and *n* and *m* the number previously attacked or not attacked, we have—

$$67{\cdot}449 \times \sqrt{\frac{1-p}{p}\left(\frac{1}{n}+\frac{1}{m}\right)}$$

for the approximate probable error of zero efficiency. It is assumed that squares of deviations from the mean values are small in comparison with the squares of the means themselves, otherwise (3) *supra* is inexact.

One then calculates the probability that such a distribution into the four subdivisions might have arisen by chance, adding some coefficient designed to measure the tendency to co-variation, or correlation, of the attributes.

This method is free of some of the more serious objections urged against the counters' scheme of our previous argument. It is quite true that the measures of improbability deduced from the tables 2A-2N are based upon theoretical reasoning perfectly akin to that involved in the deduction of the formulae of simple sampling. But the statistical " universe " sampled is different.; It is in fact the universe of "attacked" and "not attacked" ; the law of variation postulated of *that* universe is not subject to quite such damaging criticism as when employed above. In fact so far as the measure of mere improbability is concerned, the theoretical objection is rather that it somewhat *overestimates* the likelihood that the samples are homologous. Hence any results which pass this test may be. received without hesitation as something more that a mere freak of sampling a universe where the incidence of a disease is ideally equal upon the two classes compared. Hence the values of the entries in Tables 3, 4, 5 (column 11) are a sufficient rough and ready criterion of the likelihood that

TABLE 1.

Locality.	Population at Risk.	Numbers having Influenza in						
		Summer.	Autumn.	Summer and Autumn.	Winter.	Summer and Winter.	Autumn and Winter.	Summer, Autumn, and Winter.
South Shields -	462	14	27	1	31	1	3	0
Leicester - -	4,619	325	662	16	323	22	37	2
Wigan - -	1,075	45	81	1	117	0	2	1
Newcastle - on - Tyne.	4,461	277	225	4	326	39	17	2
Manchester -	4,686	709	403	70	73	26	11	3
Blackburn - -	1,284	111	82	8	83	6	10	1
Widnes - -	3,417	423	274	14	340	21	8	0
Cambridge University.	1,766	423	406	41	130	17	38	8
City of London Police.	746	50	113	4	24	0	5	0
Clifton College -	451	162	99	22	85	71	61	13
Haileybury -	515	180	73	41	106	22	25	10
Eton - - -	753	393	172	29	*	—	—	—
Harrow - -	429	90	258	29	*	—	—	—
Finchley Elementary Schools.	1,224	134	387	18	29	5	4	0

* No returns for the Winter Epidemic.

there is a real difference ; so long as the figure in this column exceeds seven or eight, we "may infer that differentiation has been rendered highly probable. To devise an average or coefficient based ultimately upon this function and comparable from sample to sample yet free from the grave objections urged against the coefficient entered in column (5) is difficult and the value of such coefficients is a matter of controversy. For present purposes we believe that the cogency of the individual results should be judged by the record of column (11)—column (12) merely translates the result of column (11) into a scale of probabilities—while column (5) may be used to compare one —experience with another but always subject to the restrictions and criticisms above noted. The significance of the remaining columns has been explained; the various " probable error " tests are of subordinate value although actually there is in the series no instance of conflict, *i.e.*, no sample which passing the imperfect test would be rejected by the more reliable one (the autumn and winter comparison of Wigan is a partial exception).

With these necessarily long yet incomplete explanations we pass to the numerical results shown in Tables 3, 4, and 5 based upon the material tabulated in No. 1.

TABLE 2A.

SOUTH SHIELDS. *Four-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−		Autumn	+	−	
Summer +	1	13	14	Summer+	1	13	14	Summer+	3	25	28
−	27	421	448	−	34	414	448	−	32	402	434
	28	434	462		35	427	462		35	427	462

TABLE 2B.

LEICESTER. *Four-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−		Autumn	+	−	
Summer +	16	309	325	Summer+	24	301	325	Summer+	39	639	678
−	662	3,632	4,294	−	360	3,934	4,294	−	345	3,596	3,941
	678	3,941	4,619		384	4,235	4,619		384	4,235	4,619

TABLE 2C.

WIGAN. *Four-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−			+	−	
Summer +	1	44	45	Summer +	1	44	45	Autumn +	3	79	82
−	81	949	1,030	−	119	911	1,030	−	117	876	993
	82	993	1,075		120	955	1,075		120	955	1,075

TABLE 2D.

NEWCASTLE. *Four-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−			+	−	
Summer +	4	273	277	Summer +	41	236	277	Autumn +	19	210	229
−	225	3,959	4,184	−	343	3,841	4,184	−	365	3,867	4,232
	229	4,232	4,461		384	4,077	4,461		384	4,077	4,461

TABLE 2E.

MANCHESTER. *Four-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−			+	−	
Summer +	70	639	709	Summer +	29	680	709	Autumn +	14	459	473
−	403	3,574	3,977	−	84	3,893	3,977	−	99	4,113	4,213
	473	4,213	4,686		113	4,573	4,686		113	4,573	4,686

TABLE 2F.

BLACKBURN. *Four-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−			+	−	
Summer +	8	103	111	Summer +	7	104	111	Autumn +	11	79	90
−	82	1,091	1,173	−	93	1,080	1,173	−	89	1,105	1,194
	90	1,194	1,284		100	1,184	1,284		100	1,184	1,284

TABLE 2G.

WIDNES. *Four-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−			+	−	
Summer +	14	409	423	Summer +	21	402	423	Autumn +	8	280	288
−	274	2,720	2,994	−	348	2,646	2,994	−	361	2,768	3,129
	288	3,129	3,417		369	3,048	3,417		369	3,048	3,417

TABLE 2H.

CAMBRIDGE UNIVERSITY. *Four-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−			+	−	
Summer +	41	382	423	Summer +	25	398	423	Autumn +	46	401	447
−	406	937	1,343	−	168	1,175	1,343	−	147	1,172	1,319
	447	1,319	1,766		193	1,573	1,766		193	1,573	1,766

TABLE 2I.

CITY OF LONDON POLICE. *Four-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−			+	−	
Summer +	4	46	50	Summer +	0	50	50	Autumn +	5	112	117
−	113	583	696	−	29	667	696	−	24	605	629
	117	629	746		29	717	746		29	717	746

TABLE 2J.

CLIFTON COLLEGE. *Four-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−			+	−	
Summer +	22	140	162	Summer +	84	78	162	Autumn +	74	47	121
−	99	190	289	−	146	143	289	−	156	174	330
	121	330	451		230	221	451		230	221	451

HAILEYBURY. *Wour-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−			+	−	
Summer +	41	139	180	Summer +	32	148	180	Autumn +	35	79	114
−	73	262	335	−	131	204	335	−	128	273	401
	114	401	515		163	352	515		163	352	515

TABLE 2L.

FINCHLEY ELEMENTARY SCHOOLS. *Four-fold Table.*

—	Autumn.			—	Winter.			—	Winter.		
	+	−			+	−			+	−	
Summer +	18	116	134	Summer +	5	129	134	Autumn +	4	401	405
−	387	703	1,090	−	33	1,057	1,090	−	34	785	819
	405	819	1,224		38	1,186	1,224		38	1,186	1,224

TABLE 2M.

ETON.

—	Autumn.		
	+	−	
Summer +	29	364	393
−	172	188	360
	201	552	753

TABLE 2N.

HARROW,

—	Autumn.		
	+	−	
Summer +	29	61	90
−	258	81	339
	287	142	429

We consider first the influence of summer attack upon the fates of the samples in the autumn wave of influenza. In five of the 14 instances, viz., South Shields, Wigan, Manchester, Blackburn, the City of London police,, and Haileybury College such difference of percentage attack rates as appears cannot be regarded as beyond the range of chance having regard to the size of the samples. In two of these, Wigan and the City police the difference of attack rates is greatly in favour of those who , had had summer influenza, but the magnitude of the epidemic was too small to enable the results to pass bur test. In the three other cases there is not even a *'prima facie* advantage on the side of the summer victims. The balance, six samples, all show a considerable and statistically significant superiority of

TABLE 3.

Summer and Autumn.

—	(1) Total investigated.	(2) Per Cent. attacked amongst those previously attacked.	(3) Per Cent. attacked amongst those *not* previously attacked.	(4) Probable Error of the Difference (2) and (3).	(5) "Efficiency" of Protection.	(6) Probable Error of Zero Efficiency.	(7) Ratio of (5) to (6).	(8) Actual Number attacked twice.	(9) Calculated Number attacked twice.	(10) Probable Error of (9).	(11) Value of χ^2 for corresponding four-fold Table.	(12) Value of P.
South Shields	462	7·1	6·0	±4·37	−18·4	±72·07	0·26	1	1	±0·60	0·02970	0·994
Leicester	4,619	4·9	15·4	±1·37	68·1	± 9·36	7·28	16	48	±4·30	26·56571	—
Wigan	1,075	2·2	7·9	±2·73	71·8	±35·40	2·03	1	3	±1·20	1·94778	0·58
Newcastle	4,461	1·4	5·4	±0·92	73·2	±17·97	4·07	4	14	±2·48	8·25467	0·04
Manchester	4,686	9·9	10·1	±0·83	2·6	± 8·21	0·32	70	72	±5·41	0·04489	0·991
Blackburn	1,284	7·2	7·0	±1·71	− 3·1	±24·40	0·13	8	8	±1·81	0·00730	0·999
Widnes	3,417	3·3	9·2	±0·97	63·8	±11·55	5·52	14	36	±3·85	16·38905	0·001
Cambridge University	1,766	9·7	30·2	±1·58	67·9	± 6·76	10·04	41	8.96	±5·81	71·77573	—
City of London Police	746	8·0	16·2	±3·59	50·7	±22·90	2·21	4	8	±1·73	2·39263	0·50
Clifton	451	13·6	34·3	±2·93	60·4	±10·90	5·54	22	44	±3·80	22·60555	—
Haileybury	515	22·8	21·8	±2·59	− 4·5	±11·69	0·38	41	40	±3·69	0·06614	0·987
Eton	753	7·4	47·8	±2·18	84·6	± 8·15	10·38	29	105	±5·91	156·70702	—
Harrow	429	32·0	76·1	±3·76	57·7	± 5·63	10·25	29	60	±3·01	62·60082	—
Finchley School	1,224	13·4	35·5	±2·91	62·2	± 8·78	7·08	18	44	±3·67	24·58404	—

25,883 298 579

TABLE 4.

Summer and Winter.

—	(1) Total investigated.	(2) Per Cent. attacked amongst those previously attacked.	(3) Per cent. attacked amongst those *not* previously attacked.	(4) Probable Error of the Difference (2) and (3).	(5) "Efficiency" of Protection.	(6) Probable Error of Zero Efficiency.	(7) Ratio of (5) to (6).	(8) Actual Number attacked twice.	(9) Calculated Number attacked twice.	(10) Probable Error of (9).	(11) Value of χ^2 for corresponding four-fold Table.	(12) Value of P.
South Shields	462	7·1	7·6	±4·84	5·9	±63·94	0·09	1	1	±0·67	0·00386	0·999
Leicester	4,619	7·4	8·4	±1·07	11·9	±12·89	0·92	24	27	±3·36	0·39572	0·92
Wigan	1,075	2·2	11·6	±2·93	80·8	±28·98	3·45	1	5	±1·42	3·70907	0·30
Newcastle	4,461	14·8	8·2	±1·17	−80·5	±13·63	5·91	41	24	±3·21	14·40079	0·002
Manchester	4,686	4·1	2·1	±0·42	−93·8	±17·41	5·39	29	17	±2·75	10·00533	0·019
Blackburn	1,284	6·3	7·9	±1·79	20·4	±23·05	0·89	7	9	±1·90	0·37152	0·93
Widnes	3,417	5·0	11·6	±1·09	57·3	±10·70	5·36	21	46	±4·31	17·05987	0·001
Cambridge University	1,766	5·9	12·5	±1·17	52·8	±10·74	4·92	25	46	±4·59	14·39117	0·002
City of London Police	746	0	4·2	±1·91	100·0	±49·10	2·04	0	2	±0·92	0·21676	0·96
Clifton	451	51·9	50·5	±3·31	2·6	± 6·49	0·40	84	83	±4·29	0·07379	0·995
Haileybury	515	17·8	39·1	±2·90	54·5	± 9·16	5·95	32	57	±4·21	24·61737	—
Finchley School	1,224	3·7	3·0	±1·70	−23·1	±34·50	0·67	5	4	±1·35	0·19650	0·96
								270	321			

TABLE 5.

Autumn and Winter.

—	(1) Total investigated.	(2) Per Cent. attacked amongst those previously attacked.	(3) Per Cent. attacked amongst those *not* previously attacked.	(4) Probable Error of the Difference (2) and (3).	(5) "Efficiency" of Protection.	(6) Probable Error of Zero Efficiency.	(7) Ratio of (5) to (6).	(8) Actual Number attacked twice.	(9) Calculated Number attacked twice.	(10) Probable Error of (9).	(11) Value of χ^2 for corresponding four-fold Table.	(12) Value of P.
South Shields	462	10·7	7·4	±3·48	−45·3	±45·88	0·99	3	2	±0·94	0·41932	0·92
Leicester	4,619	5·8	8·8	±0·78	34·3	± 9·31	3·68	39	56	±4·85	6·74839	0·08
Wigan	1,075	3·7	11·8	±2·44	68·9	±21·86	3·15	3	9	±1·92	5·04104	0·17
Newcastle	4,461	8·3	8·6	±1·28	3·7	±14·91	0·25	19	20	±2·86	0·02968	0·994
Manchester	4,686	3·0	2·3	±0·50	−26·0	±20·81	1·25	14	11	±2·25	0·67247	0·866
Blackburn	1,284	12·2	7·5	±1·98	−64·0	±25·37	2·52	11	7	±1·71	2·64963	0·46
Widnes	3,417	2·8	11·5	±1·29	75·9	±11·94	6·36	8	31	±3·55	21·00660	—
Cambridge University	1,766	10·3	11·1	±1·15	7·6	±10·54	0·72	46	49	±4·45	0·25012	0·95
City of London Police	746	4·3	3·8	±1·31	−11·8	±33·77	0·35	5	5	±1·41	0·05537	0·99
Clifton	451	61·2	47·3	±4·99	−29·4	± 7·02	4·19	74	62	±3·71	6·82973	0·08
Haileybury	515	30·7	31·9	±3·33	3·8	±10·52	0·36	35	36	±3·35	0·06092	0·988
Finchley School	1,224	1·0	4·2	±0·71	76·1	±22·89	3·32	4	12	±2·35	51·52726	—
								262	302			

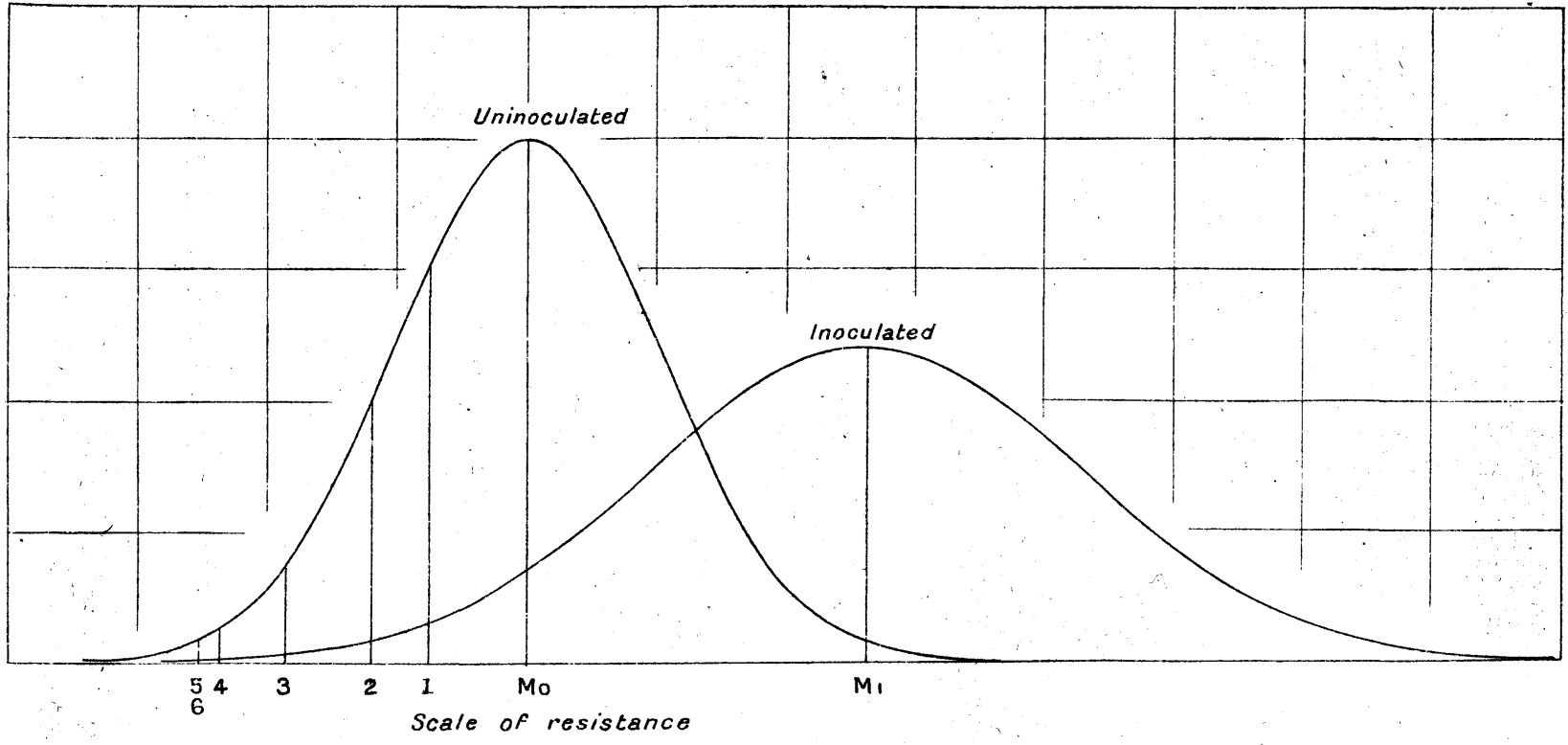
the summer patients in face of the autumn epidemic. If we average the so-called efficiencies using as weights the squares of reciprocals of the "probable errors "—we find that the average value is 54. 3 per cent, which would mean, were the severity of the different epidemics constant that the previously attacked person had only half the risk of contracting the disease incurred by his unprotected neighbour (for reasons above explained, this is a crude approximation to the unattainable truth). When we compare the winter experience of the persons attacked or not attacked in the summer, the proportion of undifferentiated samples increases ; in fact Haileybury (the single school which showed no measurable difference in the previous comparison), Newcastle, Widnes, and Cambridge University give significant values ; 36 per cent, of the samples against 57 per cent, in the previous comparison. The numerical measure of average efficiency sinks to 16.0 per cent. The autumn-winter comparison leads to results not much better than the last; four out of 11 are significant, the average efficiency 25.2 per cent.

From this comparison we may infer that, on the average, summer influenza did confer a measure of protection against the autumn and a smaller protection against the winter disease. (2) that the diminished value of the summer attacks in protecting against the winter form was not entirely a matter of the wearing out of an acquired immunity, since the autumn exposure did not confer a much greater benefit than did that of the summer, but more probably due to some immunological differentiation of the third from the first and second waves, a surmise which is concordant with the clinical experience that winter influenza was unlike that of the autumn.

Although we may be reasonably certain that the advantage —however measured—of those previously attacked is in a majority of the instances a real phenomenon, the results as a whole are unsatisfactorily discordant. Why should we find such a difference between Leicester and Manchester or between Eton and Haileybury? Had we merely been furnished with one or other set of data we should have been led to seriously erroneous conclusions as to the epidemiological importance of naturally acquired immunity, have dismissed it as of no moment or have attributed to it a general importance it is far from possessing. Before considering the matter in detail, we may meet a criticism which has no doubt already occurred to the reader.

We remarked in an earlier chapter that the age incidence of the autumn influenza was different from that of the summer, hence, in town censuses, judging immunity without reference to the ages of the exposed may lead to a fallacious result (it cannot of course do so when, as in schools, the population is of uniform age). This point was taken! early in the enquiry and it was found that a separate evaluation of age groups both at Manchester and Liecester did

(IMMUNITY.)



To face p. 144

2263.

H. & C. GRAHAM LTD LITHRS LONDON, S.E.

not sensibly modify the conclusions derived from the general tabulation of the data. No obvious explanation such as this is practicable. We have therefore to face two possibilities (1) that the wide variation of the case rates in different samples accounts for the varying results as to immunity, (2) that the biological properties of the *materies morbi* were distinct in different cases.

How hypothesis (1) might reconcile the conflicting results may not be immediately obvious ; the possibility reposes upon the following considerations.

The usual theory of immunity is that the *average* resisting power of the immunised is raised, whether by actual addition to the store of anti-bodies, as in a passive immunity, or by stimulation of the physiological sources of supply, in active immunisation, by vaccination. Were we to represent pictorially the resisting powers of unimmunised persons to varying doses of infection we might liken the group to a curve the tallest ordinate of which measures the frequency of persons of average resistance, while on either side the ordinates diminished, a very few persons are highly resistant and a very few extremely sensitive. Now if this population is exposed to the disease the number of victims will depend upon the resisting power and the virulence of the infection *(see* Diagram). One epidemic will perhaps cut down all whose resistance is less than a certain amount; measured by a point on the base line of our curve, all persons represented by the area to, say, the left of the base point fall victims, thus, in our diagram the ordinates numbered *1,2,* 3, 4, 5 correspond to epidemics of decreasing severity. In a more virulent epidemic the limiting points will lie to the right of that marking the critical value in the first case, the proportion of victims will be larger. Now let us suppose that immunised persons can be likened to a similar curve, but having its mean to the right of the mean of the uninoculated. Then if we make the same critical point of division we shall find that a smaller proportion of the inoculated or immunised will be victims than of the uninoculated provided the distribution on either side of the means is identical for inoculated and uninoculated. But if this is not so; if for instance the inoculated although "having a higher mean resistance are more variable about the mean, at some point to the left the curve of inoculated will Cross that of uninoculated and for all epidemics so mild that the critical resisting power (the point on the base line) is at or beyond the crossing of the curves, the proportion of inoculated who fall victims will actually be larger than the proportion of uninoculated. Conversely if the inoculated were less variable than the uninoculated there would be a point of crossing to the right hand, for all epidemics of greater than a certain severity the attack rate upon the inoculated would be greater than upon the uninoculated. These purely geometrical consequences, are of course: perfectly compatible with; biological considerations,

since a prophylactic measure conferring a great average benefit may place a small minority at a disadvantage. But Greenwood and Yule, who extended this conception—originally due to Maynard—to the comparison of inoculation data found no instance in which the critical point fell within the range of practical importance, the differentiation against the inoculated only commencing at (in the case of a more variable inoculated population) a mildness of attack tantamount to no real epidemic at all, thus, on the scale of our diagram, it is impossible to indicate the position of the critical point which is reached when the attack rate is less than '04 per 1,000. Still, since the theoretical possibility existed, it seemed well to test the influenza data in its light. The result of using the method described in the memoir of Greenwood and Yule cited above on the statistics of towns was to demonstrate that the discrepancies could not be interpreted in this way. The correlation of attack rates upon immunised and unimmunised, which on the theory would be very large was found to be but moderate. We have failed to reconcile our heterogeneous results in this way and reject the explanation.

We now pass to the second hypothesis.

It is known that different strains of an organism equally lethal for experimental animals may differ in their utility for stimulating the production of anti-bodies. Even in the instance of *b. typhosus*, Hooker* and Weiss,† have thought that a classification might be based upon antigenic powers. It might be that, even were the precise *materies morbi* common to two localities, its immunising efficiency varied, the Leicester strain might be more potent than the Manchester variety.

In a recent discussion of the epidemiology of phthisis ‡ Dr. Brownlee has offered reasons for thinking that epidemiologically considered the disease breaks up into three types, one having its maximum incidence upon early life, a second form prevailing in middle life, a third form chiefly affecting the declining years.

It was shown that the gross death rates from phthisis in various English registration areas could be reproduced by combining the three typical rates in different proportions, and that in those districts in which the middle-age type was predominant, phthisis as a cause of death was sensitive to variations of the social environment (overcrowding, poverty, &c). It should be understood that the analysis into three types does not imply that no young persons die of " middle age " phthisis, or that no old persons die of "young adult phthisis." The nomenclature is derived from the position of the maximum in the several types. Thus, the decennial death rate per thousand was estimated to be at age 20-25, 459 from the

---

* *Journal, Immunology,* 1916, II., 1.

Journal, Medical Research, 1917, XXXVI, 135.

‡ Medical Research Committee, Special Report Series, No, 18.

"young adult," 211 from the "middle age," and 23 from the " old age " type ; at ages 25-35 the three contributions would be at the rate of 422,365 and 36. Were two communities to receive infection of, in one, "middle age," in the other of "young adults" type, deaths would occur at all ages in both, but the position of the maximum rate of mortality would not be the same in both. From the point of view of immunity it would appear that a community chiefly infected with " young adult" phthisis might derive little or no benefit from, say, tuberculin derived from cultures of the variety of bacillus responsible for "middle age " disease ; Brownlee has suggested that a reconciliation of the conflicting testimonies as to the value of tuberculin treatment might be sought in these epidemiological results.

It is evident that, on this hypothesis, one indication of differentiation would be provided were the age distributions of attack significantly different in homologous epidemics.

TABLE 6.

Manchester and Leicester.

Age Group.	Manchester.	Leicester.*
	SUMMER.	
0–5	44	23
5–15	180	82
15–25	131	73
25–45	261	117
45 and over	93	30
Total	709	325
	AUTUMN.	
0–5	84	93
5–15	136	198
15–25	54	108
25–45	151	214
45 and over	48	65
Total	473	678

* This table has been constructed as follows :—

The Leicester rates at ages have been applied to the Manchester age groups, and the totals proportionately increased or reduced to bring the total number of cases at Leicester into agreement with the observed total. The probability that the two distributions might have arisen by sampling a common population is, for the summer pair, 30, for the autumn pair, II.

In other words, there is no strong evidence of age differentiation in attack rates as a whole, we cannot assert that the observed difference is too great to be plausibly credited to chance fluctuations.

Thus, there is a great divergence between the immunological results in Manchester and Leicester; if we found either that the two summer epidemics or the two autumn epidemics were not *in pari materia* from the point of view of age incidence, then it would be *a priori* probable that we were dealing with different epidemiological facts, and Brownlee's case would be in point. If the test of homogeneity due to Pearson* be applied to the pair of summer and also to the pair of autumn epidemics of these samples (Table 6, p. 147) it is found that the chances that what difference there is might be due to random error of sampling are quite substantial. Hence, so far as the age incidence test is concerned, no differentiation can be established. It is, however, a noteworthy fact that Haileybury College, the one public school which recorded. no sensible protection in the autumn as a consequence of summer attack, is in striking contrast to Clifton (which showed a , summer-autumn advantage) by virtue of conferring an apparently considerable immunity against winter illness. This result is explicable in terms of a type differentiation, although naturally one such contrast is not enough to prove the proposition. Since quite as great differences emerge amongst the towns or amongst the schools as separate any town from any school, it is plain that variations of immunity cannot be due to the difference of environment between an urban working class population and the pupils of a public school or to the difference between age homogeneity and heterogeneity of contacts.

It is much to be regretted that the extent and nature of our material do not suffice either to prove or disprove this hypothesis of type distinctions, since it is of capital importance. If the difference between Clifton and Haileybury or between Manchester and Leicester is not due to some methodological error and cannot be explained by some environmental cause which has escaped us, but really depends upon an essential variation of the *materies morbi*, then vaccination with the Manchester or Haileybury material derived from summer cases would have had very different results from those of the exploitation of the Leicester or Clifton material. It may even be that the variations of vaccinal results reported by different observers do not mean that all were without value and the differences merely random or explicable as gross methodological errors (which often arise by contrasting case rates derived from different stages of an epidemic).

It may be that the immunological value of the inoculant was not the same for different epidemics.† This doubt will only be resolved by a combination of experimental and epidemiological research, attention being paid to the particular biological characters of material derived from different local outbreaks.

---

* *Biometrika,* 1911, VIII., p. 250. † *Vide supra,* p. 118.

Measures have been taken to clear up this point, although we naturally hope that the opportunity for so doing, only provided by a widespread epidemic, will not be afforded.

It may now be asked whether, in view of this divergence, we are of opinion that on the average it is likely that some protection is usually conferred, whether in terms of our unproven but plausible explanation, homologous strains are commoner than heterologous strains. It is a delicate. task to pick and choose data, but had we to give a preference we should suppose that the data collected at Cambridge by Dr. S. M. Copeman, F.R.S., are most likely to represent *average* conditions. These data were compiled with especial care, the informants were educated men, and their places of exposure to risk in the summer epidemic were widely scattered (only a small minority were in residence at Cambridge throughout the epidemics). These data show a Considerable immunising power in the summer attacks, and we conclude, although with natural hesitation, that it is probable on the average that an appreciable degree of active immunity was attained by those who passed through an attack of influenza in its first and mildest manifestation. There is less evidence that the active immunity afforded by an autumn attack was of real value.

A corollary of these deductions is that, although a naturally acquired immunity is often a valuable safeguard, and its existence a justification for the further study and application of artificial immunisation, the communal value of any immunisation process is not sufficient for us to reckon it as at all likely to prevent the recurrence of epidemics in the future of the surviving generation.

We should add, with reference to the question asked by Sir Frederick Andrewes *(supra,* pp. 118-119), that the lower incidence of influenza upon the inoculated strength of the Home Forces is *not* cogent statistical evidence that inoculation did in fact confer an immunity. Three inoculations appear to have been carried out during the epidemic, and, of course, those attacked were not subsequently inoculated; the period of exposure to risk was not the same for the classes compared, being, on the average, less for the inoculated. No conclusion therefore can properly be drawn from the fact that the attack rate upon inoculated men was below the average.