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THE STATISTICAL STUDY OF INFECTIOUS DISEASES

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> " ' Yes,' said the doctor. ' Yes, I think so. It has a strong resemblance at any rate to some sort of epidemic. Probably Epidemic Hypertrophy will meet the case.' ' Epidemic ! ' said the Vicar. ' You don't mean it's contagious ? '
>
> " The doctor smiled gently and rubbed one hand against the other. ' That I couldn't say,' he said."—H. G. Wells, *The Food of the Gods*, Bk. 2, Chap. 1, Sect. 5.

UNFORTUNATELY, or perhaps fortunately, growth is neither epidemic nor contagious among adults past middle life, but the question whether a disease, or an opinion, is infectious or contagious is, as the doctor implied, not always easy to answer and has often been answered very confidently and quite wrongly. The object of this paper is to discuss what help the statistician can give in answering the question. It has interested me for years. I have not made much progress, but the account of my partial failures may stimulate quicker minds, and at least I can explain to statisticians who have not read many medical books why the problem is difficult.

It is easy to forget that words, technical words particularly, change their meaning. Thus words translated by contagion or infection were used thousands of years ago by Greek and Roman writers, but the significance they attached to them was different from that we attach to them. The first writer to use the word, or words, in our sense was Fracastorius, who was born in 1483, and published in 1543 a treatise on contagion and contagious diseases. Fracastorius was the first writer to conceive of a *living* principle of contagion and to think of the spread of a contagious (or, infectious *) disease as a biological phenomenon, due to the passing on of a living creature capable of growth, reproduction and death. Before Fracastorius, indeed long after his time, physicians and philosophers found the origin of most, perhaps all, infectious diseases in the " atmosphere." The qualities of the " atmosphere " were corrupted, the corrupted atmosphere discharged " seeds " which set up corruption in the " humours " of a living body; the corruption of these generated (or perhaps simply passed on) seeds or atoms in effluvia, mostly in the expired air or perspiration, and infected others. What these seeds or particles might be nobody enquired closely, certainly nobody thought of them as *we* think of " germs."

This is not a merely archæological digression. The point is that, unlike what we now hold to be the true doctrine, this old belief is spiritual—the seeds, like the atoms of Lucretius, or indeed the atoms of our schooldays, could not be shown on a plate. Also some, indeed a great many, victims were not (by hypothesis) infected at all from another victim, but directly by the " atmosphere."

So there was plenty of scope for disputing whether such or such a disease were infectious or not. The medical historian, Hirsch, was writing not in the seventeenth century, but a little more than sixty years ago, at the beginning of the bacteriological age. He agreed with mothers of large families that measles was a highly infectious disease, and he spoke with some asperity of those who doubted whether bubonic plague were an infectious disease. But he found no reason at all to think that influenza was infectious, and (in spite of Koch's early papers) was very dubious whether infection were of any importance in the spread of tuberculosis. It would seem strange to any reader of this story to doubt the infectious nature of either influenza or tuberculosis, and

* Strictly speaking, a contagious disease is spread by contact only, not, for instance, by the discharge of droplets. The venereal diseases are contagious, tuberculosis contagious and infectious. But the quotations in *N.E.D.* show that the terms were, from quite early times, confused.

he also knows that, in human beings, bubonic plague is not an infectious disease at all—viz., cannot be conveyed directly from one human being to another.

The explanation is not that Hirsch was a stupid man, but that his criteria were really statistical and that his statistical data—like his statistical methods—were crude.

Mothers of large families noted how measles ran through the families (their own and their neighbours'), and needed no refined statistical method to satisfy them this was an infectious disease. No doubt citizens in plague-time noted the spread of disease through a household and into adjacent households and drew a conclusion which was natural but not correct.

Even if there had been more than one John Graunt in the seventeenth century, there were no arithmetical data of the distribution of cases of measles or of plague in families of different sizes, so it would not have been possible to pass beyond general impressions.

The data are not extensive now; but, with the help of Dr. Percy Stocks, I was able to make a small statistical experiment fifteen years ago, the results of which pleased me; as they were published in a journal which is not read by general statisticians and had too algebraical a flavour to attract medical officers of health, it is fairly safe to say very few people have read them. So I permit myself an exhumation.*

The data of Table I (p. 88) (excepting the figures in brackets) relate to children under the age of 10 years who had not had measles but were exposed within the house to the risk of infection. In most instances these would be families of children, and the data are of what happened to the brothers and sisters of the first patient.

If measles were not an infectious disease, one might expect that the frequencies could be fitted by a binomial or a Poisson series. They cannot; there are far too many multiple sets. For instance, in the series for three children exposed to risk, there are 60 examples of a single infection and 27 of three infections, the binomial (taking p as the ratio of total infections to total exposed) postulates 100·9 and 6·5.

Now, however, consider what pathologists think happens. They think the disease is conveyed by droplets coughed or sneezed out by the first patient, who, however, is only infective for a very short time. Each victim is in turn infective also for only a very short time. This gives one a suggestion—why not try instead of a single binomial a chain of binomials? To make matters easy, we will suppose that all the binomials have the same p. On this hypothesis we might reach three victims in a family of 4 (that is, three exposed to risk) in four different ways.

(1) All three exposed are infected by the first victim—chance p^3.
(2) Two infected by the first exposure and then one—combined probability $3p^3q$.
(3) One from the first and two from the second exposure—combined probability $3p^3q^2$.
(4) One from each exposure—combined probability $6p^3q^3$.

Some rather lengthy but straightforward algebra enables us to equate the mean of the distribution to a sum involving integral powers of q. For instance, for 3 exposed, the mean number of cases is equal to $3 - 3q^2 + 3q^3 - 15q^4 + 18q^5 - 6q^6$. Using this device one obtains the expected frequencies given in brackets in the table. The P's range from 0·46 to 0·75 (two degrees of freedom are absorbed), which is satisfactory enough. One might do better by assuming that the p's vary along the links of the chain, but—apart from the labour—it would mean absorbing more degrees of freedom, and (owing to the decline of the birth rate) one would not have many families of more than 6. For theoretical reasons,† a chain of Poissons might be preferred, but I do not think the arithmetical results would have been much changed, and the binomial method is neat.

I have a paternal regret that nobody has used the method, but as a human being I am not much surprised, because nobody wants to verify the infectiousness of measles, and when the question is of a dubiously infectious disease we shall not have enough data to use a device of this kind. Under dubiously infectious I include not only " new " diseases (for which data will certainly be few), but diseases believed to be infectious but respecting which the vehicle of infection is uncertain.

Before embarking upon another little voyage into algebra, I propose to examine the ways in

* I cannot ask space to reproduce the rather lengthy algebra, see Greenwood, *Journal of Hygiene* vol. 31, 1931, pp. 336–51.

† Greenwood and Yule, *Journ. Roy. Stat. Soc.*, vol. 83, 1920, pp. 256–7.

which field epidemiologists, caring not at all for algebra and with no passion for arithmetic, do actually work. As an exemplar I shall choose not some classical piece—like Budd's work on Typhoid Fever or Snow's on Cholera—but the investigations of a contemporary, Dr. W. N. Pickles.*

A common—to judge from war-time experience, increasingly prevalent—disease is epidemic catarrhal jaundice. It is characterized by jaundice and symptoms occasionally alarming, but (at any rate in pre-war experience) was rarely mortal. General observations suggested that it was an infectious disease, but the biological principle, the "germ," was, and still is, unknown; there was difference of opinion on the length of the incubation period (*i.e.*, the average interval between infection and falling sick) and the vehicles of infection. It was believed that infection from person to person, as in measles, by droplets was the usual process, but transmission by other means—for instance, contaminated food or drink—was also considered.

Dr. Pickles had practised for many years in Wensleydale, knew the district intimately and kept admirable records of his experience. He had the advantage over town physicians—mentioned by Budd—that the wood was not so thick that he could not know intimately the individual trees. He had another advantage which he was too modest to mention—an intellectual affinity to John Graunt.

In 1928 this disease became epidemic in Wensleydale; in a population of some 5,700 there were 250 cases, in 118 of these the patient was attended by Dr. Pickles or his partner, and he came to the conclusion that the disease had an incubation period of from 27 to 35 days. Instead of abstracting the whole of the evidence, I shall quote in full the author's account of a connected series of 15 cases.

"Next follows what I consider my best series, especially as it includes an instance of the short and only possible exposure:—

A (the first victim)
Not attended personally, but said to have had jaundice in July 1929. It is impossible to trace the infection in his case, but it is significant that he visited Askrigg, a hotbed of infection, in June.

B (A's sister)
Commenced with the disease on August 23rd, and while still obviously jaundiced attended a village fête on August 23rd. All those on the line below were present also and developed the disease on the given dates, all 1929.

- C (Sept. 24th) B was known to have been in the house during the day.
- D (Sept. 24th)
- E (Oct. 1st) (Who spent the afternoon with B). A maid in a distant village who was proved to have been in contact with the following patients in that village who subsequently infected others.
- F (Sept. 25th)
- G (Sept. 28th)

- H (Nov. 5th) Small son of E's employer.
- J (Nov. 4th) A friend of H and E.
  - K (Dec. 8th) Brother of J.
    - L (Jan. 8th, 1930) A friend of K.
- M (Nov. 5th) An admirer of E.
  - N (Dec. 5th) Brother of M (same house).
    - O (Jan. 4th, 1930) Sister of N (same house).
- P (Oct. 27th) Great aunt of E.

"The five names on the third line are those of the only sufferers from jaundice in the whole district who commenced in the week September 24th to October 1st. Three of these were from the village in which the fête was held, and I found, as I expected, that they had all been present on August 28th. I felt sure also that I was on the track of an interesting discovery

* W. N. Pickles, *Epidemiology in Country Practice*, Bristol (John Wright), 1939, pp. 114.

when it transpired that the other two from distant villages had this, and only this, experience in common with those three. Someone suffering from jaundice, therefore, had also probably been a visitor at the fête. I tried various sources, and at last, after a long search, I discovered the culprit where I least expected, almost on my own doorstep.

" This was a young girl (B) whom I had actually seen in bed on the very morning of the 28th, and who I never dreamt would be able to get up that day. I have no doubt she exercised considerable skill and elusiveness at the entertainment, for I was also among the throng, and did not know of her presence. This girl had as a friend another girl of 16 (E), who lived in a distant village, and these two girls spent the afternoon together, with the result that E herself commenced with the disease on October 1st, and, as can be seen in the diagram, infected four others in this village. She was employed as a maid, and she infected her employer's small son, this boy's friend, and her own great-aunt, who lived in the village. The infection in all these was easy to explain, but in the fourth (M), a rather pathetic little fellow of middle age, it was not so clear. At last I tackled his sister, who gave him away quite shamelessly. Studies in epidemiology sometimes reveal romances. ' Oh, yes,' she said, ' he's very fond of E. He often goes in at the back door in the evenings, and helps her to wash up.' The brother of M in the same house commenced on December 5th, and the faithless sister, above mentioned, with poetic justice succumbed on January 4th. J, who was a friend of H and E, commenced on November 4th, his small brother on December 8th and this small brother's friend on January 8th. Thus, to my knowledge, thirteen instances of this disease resulted from the determination of one young girl, jaundice or no jaundice, not to be deprived of what she considered her legitimate amusement."

TABLE I

Frequencies of secondary cases of measles in groups of 2, 3, 4 or 5 children exposed to risk, compared with the expectations of chain-binomials (bracketed figures)

Cases *	(m = 2)		(m = 3)	
0	197 (198·3)	120 (122·4)	84 (89·7)	37 (40·8)
1	104 (101·4)	93 (88·2)	60 (52·7)	34 (27·9)
2	57 (58·3) P = 0·75	86 (88·4) P = 0·58	57 (54·4)	42 (42·7)
3	— —		27 (31·2) P = 0·36	36 (37·6) P = 0·42

	(m = 4)	(m = 5)
0	60 (59·54)	25 (26·86)
1	29 (28·87)	15 (12·42)
2	25 (24·45)	9 (10·63)
3	11 (14·35)	10 (6·90)
4	7 (4·79) P = 0·61	1 (3·30)
5	— —	1 (0·89) P = 0·42

* In the two smaller series only children with *no* previous history of measles were included.

I used to tell my students that field epidemiology was like detecting criminals; but there are not many epidemiologists who can write like Dr. Pickles.

In all Dr. Pickles had 40 instances of patient-to-patient spread; in 6 the interval from case to case was 26 days, in 6, 27 days, in 5, 28 days, in 7, 29 days, in 5, 30 days, in 5, 31 days, in 2, 32 days, in 1, 33 days, in 2, 34 days and in 1, 35 days.

I do not think it necessary to use paper in demonstrating that Dr. Pickles has established a *very* strong case in favour of his contention that the incubation period of the disease as observed in Wensleydale was about a month and, of course, that it was infectious. But, if the layman thinks he will often find in the literature of epidemiology such pretty demonstrations, he will be disappointed. There are many reasons for this. I have mentioned two: ability to do such an investigation is rare, and in a great town it is not easy to simplify human relations; the clues are tangled up. That may happen even in the country when the epidemic is overwhelming (as in influenza) and the incubation period short.

Here again, however, chance will favour a prepared mind, Dr. Pickles' mind.

> " For instance, a few years ago a farmer spent a night in Birmingham, having travelled this distance to bring back a new car. He commenced with influenza a short time afterwards, infected his family, and they in turn a large village. Again, a few years ago, a particularly worthy schoolmistress returned to her home after a Christmas holiday spent with her relatives. On the morning of the school opening, knowing that she was ill, with commendable if mistaken zeal, she attended her school. In the afternoon she was utterly unable to return, but from that brief morning session a crop of 78 cases resulted. I did not realize this myself until I examined my chart afterwards, and with the exception of one case, which might possibly have been derived from a neighbouring town, there was no other conceivable avenue by which the epidemic could have reached the district."

Of course all field epidemiologists do proceed on Dr. Pickles' lines, but, to use the detective analogy, they are like Scotland Yard inspectors sent down when a crime has been committed, suspects numerous and the scent cold. I am not thinking of water-borne or food-borne diseases—in that department *ex post facto* enquiry has often been decisive—but of the kind of disease so far illustrated where transmission from person to person is, *a priori*, the most attractive hypothesis. It is often possible to connect one case with another—or to show, on a spot map, or series of spot maps, what looks like radiation from foci, such as schools. But it is not easy, in fact it is sometimes impossible, to establish connections. One is particularly conscious of this in studying the literature of Acute Poliomyelitis (epidemics of what used to be called infantile paralysis); the most diligent enquiry often fails to establish any human connection (or any common consumption of food) linking together foci widely separated.

But let us suppose a connection is established, and use Dr. Pickles' data as an illustration. Take two of the chains in his diagram, the EMNO series and EJKL series. We have the case dates, October 1st, November 5th, December 5th, January 4th, in one set and October 1st, November 4th, December 8th, January 8th in the other. Taking October 1st as origin, the succession is 0, 36, 66, 96 in one and 0, 35, 69, 100 in the other. The intervals between successive cases are 36, 30, 30 and 35, 34, 31. The connection was actual contact, and what specially interested Dr. Pickles was the uniformity of the intervals, all six between 30 and 37. If one took at random a couple of points on a line 96 units or a line 100 units long, the average intervals formed would be respectively 32 and 33·33 days, but all lengths are possible from 0 to 96 or 0 to 100—if for instance one point fell at 0 and another at 96, then the three intervals would be 0, 96, 0; there is no reason why they should fall within a narrow range about the average. So one might enquire whether the variance of the intervals were smaller than could be reasonably expected as a result of sampling when the points actually had been taken at random. When only two points are in question, this is a soluble problem (see p. 99), the probabilities of random sampling producing variances so small as in these two trials are 0·09086 and 0·05441. A combined probability of 0·0049.

With the other evidence before us, this is a mere slaying of the slain; but, as already said, one does not find in epidemiological literature many such neat demonstrations, so it is at least worth considering whether by a study of the distribution of intervals the statistician can give the epidemiologist any help. In an appendix I have summarized what I could find in the literature or work out for myself on the algebra and arithmetic of interval-distributions; it interested me, but whether it *is* of any use needs careful consideration.

Let us begin with the simplest case. Over a period—a month, a year or what period we please—n cases of disease or n deaths have occurred in a house, family or institution, and we know the dates of occurrence. By one or other of the methods described in the appendix we can determine the probability that the frequency distribution of intervals (or some parameter such as the variance) might have arisen in sampling a random succession. Let us suppose that calculation establishes that the hypothesis is improbable and should be rejected; is this finding of epidemiological value? Very often it will be of no value whatever, it will be mere arithmetical trifling. We do not need to do any sums to satisfy us that the distribution of intervals between successive deaths from enemy action in vulnerable areas is not a random distribution. Unless we can go farther than this we shall not be helpful to the field worker.

One of the most interesting examples in epidemiological literature of only partly solved problems is that of epidemic poliomyelitis or, to give it the popular name, infantile paralysis. As *a clearly*

recognized epidemic disease, this has not a very long history; indeed, in our country it has only attracted serious attention since 1910, although both Sweden and the United States of America had serious epidemics in the previous decade.

The fundamental biology of the disease is well known, viz. that the *materies morbi* is a virus, which may be conveyed from person to person by droplet infection—discharging of infective particles in coughing or sneezing—or by contamination of food. Study of the literature shows that the earlier writers gave droplet infection the first place, but recently opinion has moved in the direction of emphasizing the alimentary route. For instance, McAlpine * has examined the incidence of poliomyelitis on the troops in the Indian Command during the war. He points out that British officers suffered a much greater incidence than other ranks—British or Indian. In 1942, the attack rate on British officers was 1·7 per 1,000, in 1943, 0·5, and in 1945, 1·4. Other British ranks had incidences of 0·3, 0·1 and 0·3; Indian troops a rate of 0·01 in each year. He attributes this differentiation to poor sanitary supervision of officers' messes and, of course, of the civilian restaurants, which they use much more generously than other ranks.

Pearson and others † record a thorough investigation of families in Fort Worth, Texas, at the time of an epidemic. Here is a summary of their results:—

> "During the 1943 epidemic of poliomyelitis in Fort Worth, an intensive study of the distribution of virus was made in a selected district of the city. Stools from 524 persons were tested for virus by inoculation into monkeys. Six (75 per cent.) of 8 households, representing 27 familial contacts, were positive for virus, as were 8 (18 per cent.) of 45 households containing 80 non-familial contacts and two (1·6 per cent.) of 127 households representing 374 non-contacts.
>
> "Virus was not recovered from specimens of water, sewage, flies, ants, cockroaches or droppings of domestic animals.
>
> "An agent that produced paralysis in mice and cotton rats was obtained from a pool of brains and intestines from 22 Norwegian rats from the city dump. No virus was recovered from several batches of mice and rats collected in various parts of the city."

The inference is that intra-domestic contamination of food *may* be an important means of spread.

It is certain that, in comparison with such diseases as measles, whooping-cough, scarlet fever or diphtheria, infantile paralysis spreads, at any rate as a recognizable illness, slowly. But sometimes it is a real scourge: there are a large number of cases in a small population. Here is an example of a dramatic incident observed during the epidemic of 1911 in South-West England. The hamlet of Stoke Rivers consisted of 18 houses with a total population of 119, and among these 36 attacks were recorded. Only 4 of the houses had no patients and 1 house with 13 inmates 9.

In the epidemic in Sweden of 1905 in a small parish (Trästena) with 500 inhabitants, 49 persons were affected, 26 of these with the paralytic form of the disease—of these 11 died.

A catalogue could be made of grim incidents like this. There is, as might be expected, a goodly list of papers and reports on the subject, but they contain few, in fact hardly any, data like those Dr. Pickles gave us for epidemic jaundice. Sometimes one can find chains of cases in families, schools or institutions, but I have not been able to collect a sufficient number to provide material for the application of the method described in the appendix to this paper to be of any practical use.

The papers I have found most stimulating are two by Aycock and Eaton.‡ In the first place the authors made frequency distributions of the intervals between the first and subsequent cases in the same family (Table III). Of course, if there were more than two cases in a family, that family would contribute more than one entry into the table, and how often that happened is not stated, but it appears from other evidence that there were few instances of three or more cases in a family, so that a great majority of the entries are records of pairs.

The authors also supplied a table of frequencies for scarlet fever and measles. No calculations were required to convince one that the infantile paralysis series was not *in pari materia*

* *Lancet*, 1945, ii, p. 130.
† *Amer. Journ. of Hygiene*, vol. 41, 1945, p. 188.
‡ *Amer. Journ. Hygiene*, vol. 15, 1925, pp. 725–41

with those for measles and scarlet fever. One also finds that the combination of cases of the grave form of disease, where the victim has paralysis of some group of muscles, with mild cases leads to an ambiguity.

> " The difficulties in the recognition of abortive cases of infantile paralysis are well known. The presence of a paralytic case undoubtedly influences the diagnosis. It is our impression that this influence decreases as time elapses from the appearance of the paralytic case; that is, if an indefinite illness, say, a digestive upset with slight nervous symptoms, occurs within a few days of a frank case of infantile paralysis in the same family, its chances of being called infantile paralysis are much greater than if it had occurred some weeks earlier or later than the paralysed case." *

TABLE II

Incubation Periods for Experimental Inoculations of Infantile Paralysis in Monkeys

(Aycock and Eaton)

Period from inoculation in days	Frequency	Period from inoculation in days	Frequency	Period from inoculation in days	Frequency	Period from inoculation in days	Frequency
3	3	10	22	17	3	24	0
4	17	11	25	18	1	25	0
5	30	12	12	19	0	26	0
6	33	13	11	20	2	27	1
7	42	14	7	21	3		
8	37	15	4	22	0	Total	286
9	30	16	0	23	3		

The authors also provide a table of the interval elapsing between the experimental inoculation of the virus and the appearance of physical signs of disease in monkeys. (Table II.) Aycock and Luther have also collected † data of intervals between exposure to risk of infection and onset of disease in human beings, and this evidence is consistent with the opinion that the incubation period is not less than 7 days and, on the average, more. This work was done some time ago, but I do not think we have any more published statistical evidence of the kind.

TABLE III

Infantile Paralysis. Interval between initial and secondary case in same family.

(Aycock and Eaton)

Locus	Interval in days																		
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Sweden 1905	12	22	15	14	11	7	9	7	5	5	5	1	2	(Over 12 days 12)					
New York City 1906	61	45	47	41	46	45	26	17	22	9	8	7	3	3	2	1	3	3	2
Massachusetts 1916	10	21	18	20	12	14	16	14	13	(Over 8 days 54)									
Aycock and Eaton's series:																			
Total	40	46	34	29	28	19	23	27	15	6	2	4	5	4	4	6	4	1	0
Paralysed	9	17	17	12	14	8	10	15	10	1	1	3	4	2	3	3	3	1	0
Abortive	31	29	17	17	14	11	13	12	5	5	1	1	1	2	1	3	1	0	0

This is the position; none of the secondary cases with intervals not exceeding 6 days can, so it appears, have been derived from the primary cases, the patients must have been infected in some other way. But *some* of the patients whose cases were at intervals of more than 6 days from the first cases in family may have been infected within the family. *What* proportion? Suppose one has n pigeon-holes numbered from 1 to n, there are n^2 ways in which two can be independently chosen; in n of these the choice will fall on pigeon-holes with the same index, in $2(n-1)$ there will be a difference or interval of 1, in $2(n-2)$ a difference of 2, and so on. In the table we have

* *Op. cit.*, p. 727.

† *Journ. of Preventive Medicine*, 1929, vol. 3, p. 103.

series collected by Aycock and Eaton. A rough test of independence would be to find that zero intervals were about half as numerous as unit intervals; this is so for the Swedish, Massachusetts and Aycock and Eaton's " paralysed " series. Taking the latter, one finds that for n from 12 to 14 the " fit " for independence is quite reasonable—a P of about 0·25—but the tails will not fit. We can " explain " in this way about 88 per cent. of the secondaries. But the data are too sketchy and heterogeneous. One wants not aggregated figures, but separate family records—hundreds of short series to which the methods I have suggested in an appendix (or improvements of those methods) can be applied. These data exist, in the files of public health departments, but have never been published.

It is only human that an investigator should try to solve his particular problem—viz., to explain how infantile paralysis really was disseminated through Great Puddleton—whether the Council School, the milkman or, perhaps, little XYZ, or even a fly did the deed. But usually, perhaps always, one can do no more than show how the disease *might* have been spread.

Sometimes an investigator is perplexed. Dr. Jönsson, for instance, a Swedish investigator * having made a table of contacts between children who took the disease and children affected earlier, reached the following results. Of 272 cases, in 59 there had been contact in school, in 20 in the household, in 12 repeated contact outside school or home and in 10 chance contacts, leaving 171 where no contact was discovered. He then, on the advice of Professor Dahlberg, made a control experiment. For each child in the series of cases he took, from a card index of the district, a " control " child and worked out its contacts with patients. This gave him 44 school, 3 household, 18 repeated, 16 casual and 191 no-contacts. Jönsson was rather disappointed; he concluded there was not much difference. Actually if one combines the figures into a 2 by 4 contingency table, the value of P for 3 degrees of freedom is very small. But if we make a 2 by 2 table—compare contacts of some kind with no-contacts—there is no significance, and the author, who knew his material, attached very little importance to the great disparity between household contacts. I do not feel sufficiently sure about the way the experiment was done to be able to reach a conclusion, but it does suggest the advisability of not over-emphasizing the truism that " oft the means to do ill deeds makes ill deeds done."

The way infantile paralysis spreads through a community still seems obscure. What *does* seem certain is that infantile paralysis, like—on a large scale—cerebro-spinal fever and influenza, has increased in importance during our generation. I hope we statisticians may be able to do something about it; we need more data.

So far, I have examined the statistical problem from a point of view which, if not novel—there are few novelties in points of view, for statistics is an old science—is not often taken. I have thought of the statistical universe not as an aggregation of cases, but an aggregation of sets of cases. I have not made much of it, but hope to have suggested to younger statisticians, both field workers and mathematicians, trains of thought. I pass to a review of more familiar work, based on aggregations of cases or deaths. One may study the vicissitudes of infectious disease over many years in a great city or even a nation and try to discover the " law " of change. Again, one may select particular outbursts or epidemics, statistically analyse each of these and again seek uniformities and contrasts.

In our own country the pioneers were William Farr, John Brownlee and Ronald Ross. Nobody will doubt that two of these names are immortal and, in my opinion, Brownlee, of whom older fellows of our Society have kindly memories, had a spark of genius which the smoke of a too philosophical exposition did not permit to give as much light as it should have given. The three were, psychologically and through education, very different people. Farr was primarily a statistician with, as Brownlee once said of him, a genius or intuition for discerning the essential truth behind a statistical table. Brownlee, the only one of the three with the advantage of a university education in mathematics, had had wide clinical experience of infectious diseases and was as erudite as Creighton. Ross, a self-taught mathematician, had, as we all know, a wholly unrivalled first-hand knowledge of malariology.

Farr's contributions to the subject were not numerous, and are concerned with particular problems of the rise, decline and fall of an epidemic as an isolated event. He did not, so far as

* B. Jönsson, *Zur Epidemiologie der Kinderlähmung*—Supplement 98 to *Acta Medica Scand.*, 1938, pp. 125 *et seq.*

I remember, do any arithmetical work on secular changes. We do not *know* what led him to formulate his two " laws," but one can make a reasonable guess.

He no doubt started with the belief—uncontradicted by experience, otherwise this paper would not be written—that epidemics, however menacing, do come to an end, and the hope which we still have, that it might be possible early in the course to predict when the tide *would* turn. Farr, who was always interested in actuarial science, was surely well acquainted with the simpler methods of graduating rough series used a century ago. Perhaps he began by differencing the weekly scores of deaths, or cases, found that the higher differences did *not* tend to constancy, and then tried the method on the logarithms of the frequencies. There he found that there was *some* hint of convergence. His first epidemic " law " was that the second difference of the logarithms was a negative constant; his second " law " that the third difference was a negative constant. Farr did not perceive that a solution of his first difference equation was the normal function; that was first pointed out by Brownlee, and it was Brownlee who first called attention to Farr's work just 40 years ago.*

Brownlee's ultimate views were formulated in a paper, which appeared a few years before his death, in a medical journal; † a precis of these may be useful because the transactions of a medical society are not familiar ground to statisticians (Appendix 2). Of his work on secular changes, on periodicity, I need say nothing, because much of it appeared in the *Philosophical Transactions.*

Ross's work, most of which was published in the *Proceedings of the Royal Society*, is readily accessible to statisticians.‡

The differences in method of approach of the two investigators are these. Brownlee began empirically—viz., by graduating many recorded epidemics with Pearsonian curves; few of them were perfectly symmetrical, although some did approximate to the Gaussian form. He himself was much impressed by the fact that *if* the infectivity of the disease decreased in geometrical progression from the start of the epidemic, then Farr's first " law " held. He thought that deviations from this norm, which he regarded as, in Plato's sense, the pure idea, were imposed by a great variety of circumstances.

Ross started with the conception of a group the strength and constitution of which were subject to variation in many ways; at the beginning of observation there would be so and so many persons healthy, so and so many suffering from a disease, so and so many recovered from it, of whom some would be immune, some again susceptible. The group would be subject to immigration, natality, mortality, relapse, etc., etc.

In his first studies Ross used the method of differences. So long as one took the various rates as constants, the task was simple. Some readers may remember an illustration in a student's textbook, Runge's *Theorie und Praxis der Reihen*,§ one reaches a system of homogeneous difference equations of the first degree with constant coefficients. If, however, the rates are functions of the time, algebraical difficulties may become formidable. The difference or differential equations set up are not always easily solved and, when solved, not easily tested on available data.

Ross and his successor, the late Col. A. G. McKendrick, a mathematical statistician whose excellent papers are well known to fellows of the Society, were tackling a more general problem than that Brownlee had in mind, so inevitably their results were more complex. To the empiricist, the working statistician, it may be that these investigators have given food for thought rather than working tools. But the steady increase of mechanical aids to computation is making it possible to try out methods before the labour of which an older generation would have quailed.

To those who, like me, take more pleasure in arithmetic than in algebra, the late H. E. Soper's paper in our *Journal* is a source of inspiration.‖ Soper's object was to test whether the apparent periodicity of epidemics of measles could be effectively described in terms of the hypothesis that the flux and reflux of measles were due to the replenishment of the susceptible population after an epidemic had killed or immunized those then present and susceptible. On the elegance and simplicity of Soper's technique I need not dwell; it is enough to say that it was worthy of Soper.

* *Proc. Roy. Soc.*, Ed. 1906, vol. 26, pt. vi, p. 454. *Brit. Med. Journ.*, August 15th, 1915.

† *Proc. Roy. Soc. of Med.* (*Sect. Epidem. and State Med.*), February 1918, pp. 85–132.

‡ Ross reprinted these papers, with some additional notes in a booklet, *A Priori Pathometry*, by Sir Ronald Ross and Hilda P. Hudson. London, 1931 (Harrison and Sons).

§ Leipzig, 1904, pp. 51–6.

‖ *Journ. Roy. Stat. Soc.*, vol. 92, 1929, pp. 34–73.

I propose now to speak briefly of the results yielded by the application of some of these methods to the data of observation, and to end with an even curter reference to the experimental work in which I collaborated for so many years with Topley and other friends.

The easiest kind of epidemic to have clear in one's mind's eye is that generated by the contamination of a source of food or drink common to a large number of persons. A beautiful example is " The Case of the Methodist Ladies." * On the occasion of a fair in a small Californian town (Hanford), some ladies became amateur caterers and provided, among other good things, an excellent dish of spaghetti which was much appreciated. Unfortunately one of the ladies was a " typhoid carrier "; the dish was succulent and a culture of typhoid germs; of 150 guests, 93 went down with typhoid fever.

Here the " curve " or " law " of the epidemic *ought* to be a reproduction of the frequency distribution of the incubation period of typhoid fever and analogous to that of an experimentally inoculated disease—viz., to the data of experimental poliomyelitis quoted earlier. There will, of course, be blurring, because the guests, unlike the monkeys, will not all receive the same dose. Miner † extracted from the literature the above-mentioned and some similar examples—viz., other examples where there was one opportunity of massive infection—and confined his statistical study to the persons who had, so far as was known, only this opportunity of becoming infected. The result was that, although the means varied, the curves were similar—viz. (like the poliomyelitis data) positively skew with a long tail to the right. In his best set, a Pearsonian Type 1 curve with $\beta_1 = 0{\cdot}6538$, $\beta_2 = 3{\cdot}393$ and skewness $= 0{\cdot}65$ gave a good graduation.

This is well enough, and perhaps we might go so far as to say that if an epidemic of uncertain ætiology is positively skew with β's not *wildly* different from 0 and 3·0, its form is consistent with that of the frequency distribution of the incubation period; so massive infection within a short interval is a hypothesis seriously to be entertained. But any statistician with experience of curve fitting, who therefore knows that wholly disparate equations may produce graphically indistinguishable forms, would decline to go farther.

The next class of epidemics respecting which one has statistics on a large scale is concerned with diseases in which mass infection in the sense of the last paragraph does not occur. The most closely studied example is plague. Brownlee studied the forms of no less than 64 epidemics in great cities ranging in time from 1563 to 1913 and in place from London to Hong-Kong. Although only in rather more than half (36 out of 64) was β_1 less than 0·1 and in 4 greater than 0·5, he was, I think, justified in holding that the form was symmetrical and could be expressed by what he emphatically called the " epidemic curve." This would arise (see Appendix 2) if the following conditions were fulfilled: (1) The number of persons infected during an epidemic is so small in relation to the total population that the supply of susceptible units never becomes appreciably less. (2) Infectivity is very high when the epidemic begins and from the beginning declines in a particular way, which is expressed by the product of a term in a geometrical progression and a power of the number of new cases in a time interval.

Plague in human beings is usually an epiphenomenon of plague in rats, and Brownlee passed to the study of plague in rats, using the results of trappings in twelve districts of Bombay (1905–6). Here one has data not of deaths, but infections. In both species of rat—the house rat (rattus) and the sewer rat (decumanus)—the β's fluctuated a good deal, but the averages for the whole city were 0·070 and 3·159 for rattus; 0·038 and 3·499 for decumanus. The " obvious " explanation of a decline in first the epizootic then the epidemic is that not enough susceptible rats are left alive to keep them going. Brownlee's rejoinder is as follows:—

> " On the theory that the epizootic dies out from want of a sufficient number of susceptible rats, it must be shown that statistically this is compatible with the facts. The data are simple. On the one hand, after the epidemic of plague is over, about a third to a half of the rats at least are found to be still susceptible to plague; secondly, the proportion of black rats affected is only about one-half that of the brown rats. As the evidence is in favour of equal susceptibility to plague in both species under like conditions of infection, this difference must be due to the facilities for infection being smaller in the case of the black rat than of the brown rat, and has been explained on the ground of the observed fact that the number of

* See *Plague on Us* by Geddes Smith (New York, 1941), pp. 209 *et seq.*

† J. R. Miner, *Journ. Infect. Dis.*, vol. 31, 1922, pp. 296–301.

fleas on the brown rat is twice as great as that on the black rat. Either of the sets of facts regarding the black or brown rats might easily be explained on the theory that the epizootic ends because the population of susceptible rats is not sufficient to maintain it. As far as I can see, however, at the present moment, the data regarding the two epizootics are not easily adjusted so as to be mutually reconcilable. In the appendix I give a diagram with a table of constants of the forms of epidemics which may occur on this hypothesis. The constants include the infectivity assumed, the values of β_1 and β_2, the number of susceptible units out of each initial thousand units remaining uninfected at the end of the epizootic and the standard deviation. The form of the epidemic among the brown rats closely corresponds to that shown in the diagram as being due to an infectivity per infected unit of 1·6, the value of β_1 being in this case small, the value of β_2 3·58 approximately that given by the observations, namely, 3·50, and the proportion of susceptible units left uninfected, 30 per cent. of the original number, a number sufficiently close to the facts for all practical purposes. If it is now assumed that owing to inferior power of transmission of the disease a lower degree of infectivity exists among the black rats, and that the proportion of black rats affected is half that of the brown rats, the infectivity among the black rats must be in the neighbourhood of 1·2, which would satisfy the conditions—namely, $\beta_1 = 0$, $\beta_2 = 3{\cdot}16$. The epidemic in the black rat would, however, require to have a standard deviation in proportion to that of the brown rat of 8·4 to 3·2, whereas the actual values are respectively 2·53 and 2·45. Further, if the theory held, the epidemic in the black rat would culminate very much later than that in the brown unless some other circumstance interfered to suddenly terminate the epizootic. But such a sudden termination of the epizootic implies great asymmetry, and the data are in direct opposition to the possibility of this great asymmetry. Closer approximations to the maxima of the two epidemics in time might be found by taking the infectivity among the brown rats as initially higher, but in this case $\beta_1 + \beta_2$ assume higher values, values quite out of the range of those found from the statistics.

" On the other hand, on the theory of the loss of infectivity on the part of the infecting organism the whole facts are easily explicable. It furnishes an explanation of the symmetry and also of the near synchronism of the two epizootics, while the difference in the number of fleas provides a basis for expecting that the concentration factor already alluded to should be different in the epizootics of the brown and the black rat." *

The statistical argument is, I think, cogent, but if, encouraged by its lucidity, we entertain hopes that the " epidemic curve " is a statistical master-key, a much earlier paper by Brownlee † chills us. In that paper he has fitted Pearsonian curves to 40 epidemics, including the epidemics of influenza (deaths) in 1891 and in 1891–2. For the former the β's are 0·6342 and 4·5863, for the latter 1·2217 and 5·7329. I have taken out the figures for the first wave of the great epidemic (London) of 1918 (the weekly deaths used were 5, 10, 67, 218, 287, 192, 86, 38, 21, 20, 12). The β's are 0·93317 and 4·55778. Neither " the epidemic curve " nor constant infectivity with exhaustion of susceptibles will do at all.

Perhaps a young mathematical statistician will conclude that a systematic algebraical formulation of the consequences of different biological ways in which infection *may* wax and wane in a community, more rigorous and, arithmetically, more efficient than those I have indicated, is within his power. But he will certainly want to know, before undertaking a heavy piece of work, how much real evidence the " doctors " have in favour of (or against) their pet theories. It will have been clear that Brownlee, for instance, believed that changes in the biological properties of the living, infective material were the prime cause of epidemics. So long as we remain in the pleasant land of analogies, a plausible argument can be sustained.

Most educated people know that the properties of " germs " can be altered by passage through living bodies, that a strain may have its virulence—its killing power—increased, or decreased a hundred-fold in this way. Why should not this happen in " nature "? Suppose, for argument's sake, that the virus of influenza is a normal guest of or parasite upon human mucous membranes. This living creature's reproductive cycle is shorter than that of a metazoon. Well, just as at intervals of a century or so a Bonaparte or a Hitler emerges, so may a virus emerge which causes a holocaust and, like a Bonaparte or a Hitler, decays.

* Brownlee, *op. cit.*, pp. 98–9.

† *Proc. Roy. Soc. Edin.*, 1905–6, pp. 485–521.

This is well enough, but have we *proof* that such things do happen? In collaboration with the late Professor Topley, with Professor Bradford Hill, with Dr. J. Wilson and other colleagues, I have studied the biostatistics of epidemics in herds of mice over a period of more than 10 years. Our principal results were summarized in 1936.* I can resist the temptation of vanity to write at length on this work. If I go to the opposite extreme and seem to dogmatize, all the evidence is accessible.

Virtually all reasoning, from mice to men, is analogical; a herd of mice under the environmental conditions of our experiments is a slum inhabited by cannibals, having just two advantages over Belsen: (1) the inhabitants are abundantly fed; (2) none are deliberately tortured. In our terminology virulence means power to kill, if a measured dose of the germ inoculated into, say, 25 animals kills 20 of them, we should say it was highly virulent. By an infective strain we mean one which spreads a disease under the following conditions. A number of mice, 25, are inoculated with the strain and housed with 100 normal mice for 60 days; if a large proportion of the latter take the disease, whether they die of it or not, we should call the strain infective. The following account of a particular set of experiments shows that the infectivity of a germ may change during the epidemic spread of the disease.

TABLE IV

	Strains				
	P.M.$_3$	P.M.$_3$(2)	P.A.39	P.A.39(2)	P.62
No. inoculated	25	25	25	25	25
No. inoculated that died	20	20	25	21	25
No. contacts	100	100	100	100	100
No. contacts that died	12	3	13	13	62
No. contacts that died showing *Past.* P.M. ...	0	0	6	3	50
No. surviving contacts	88	97	87	87	38
No. survivors showing *Past.* P.M.	0	0	0	1	7

On 6.4.1932, 25 mice were inoculated each with 100,000 *Pasteurella* of a strain that killed 20 out of 25 when inoculated intra-peritoneally with this dose. The 25 were housed with 100 normal mice, and 9 days later one of these died of pasteurellosis; in the following week there was no further spread and 25 more infected mice were added; by 4.6.1932, 11 added mice had died, although the organism was only recovered from the tissues of 8. From this time a small wave of disease began and between 4.6.1932 and 13.6.1932, 30 added mice were dead. At this point we began to add 3 *normal* mice daily, but the mortality subsided, and in the two months ending 15.9.1932 only 18 died in the cage, most of which were devoured, so we had no *post mortem* evidence of infection.

The population was now increasing rapidly, so immigration was stopped. The day after this edict a mouse died of pasteurellosis. The strain recovered from him was injected into 20 mice on 23.9.32 in the usual dose of 100,000 organisms and these 20 mice were added to the herd. On 1.10.1932 the epidemic began to spread, and continued to do so; on 23.10.1932 immigration of 3 normal mice was resumed and the mortality maintained, and until the experiment was discontinued, many months later, the rate of mortality only showed minor fluctuations. So there were three phases: a slow beginning, a flare up of disease which soon burned itself out and then a second and really effective dissemination.

Five strains of the organism were isolated and used in the subsequent experiments:

P.M.$_3$. The original strain.
P.M.$_3$(2). The same strain after repeated subculture.
P.A.39. A strain isolated from a contact mouse dying in herd during the period of abortive spread.

* *Experimental Epidemiology* by Greenwood *et al.*, S.R.S. No. 209 of Medical Research Council, pp. 204, London 1936, S.O.).

P.A.39(2). The same strain after repeated subculture.
P.62. A strain isolated from the herd during the final period of effective and continuous spread.

With each strain 25 mice were inoculated and herded with 100 normal mice, and each community was observed for 60 days. On the sixtieth all survivors were killed and cultures taken from heart and spleen. All mice dying were examined *post mortem* unless cannibalism prevented this. The results are shown in table IV.

P.62 is differentiated from the others; it was both virulent and infective. A fair inference is that the phase of effective and continuous spread in herd was due to the appearance of a variant which had retained virulence and acquired infectivity.

There is, then, an observational basis for Brownlee's doctrine. When one looks back at a piece of research, one always wishes something had been done differently. We might have repeated these studies, have made them a part of the routine. But this was only an item in our programme, there was much else to do. Experimental epidemiology is time-consuming and mice-consuming. It has *not* been proved that Brownlee's theory always holds.

In one experiment too long to be described * we had no proof that a devastating epidemic of a virus disease was associated with any change of virulence or infectivity. All I conclude is that Brownlee's hypothesis is not merely whimsical. If it is true, why, or rather how, is infectivity enhanced? The riddle of the epidemiological Sphinx is still unread. At the end of the war of 1914–18 the world suffered its greatest epidemiological catastrophe since the fourteenth century, and it was human to think that the miseries of war had something to do with it. We have no proof. At present human misery almost as intense as during the Thirty Years' War is more widespread. That there should be killing infectious diseases due to overcrowding and dirty feeding is a rational expectation. Will there be something much more deadly and widespread—in fact a pandemic of influenza like, but greater than, that of the autumn of 1918? The researches I have described do not give an answer. They do suggest to me that if the rising generation of statisticians, whose mathematical training has been more thorough than that of the pioneers, will give their attention to the problems of statistical epidemiology, a veteran reading a paper here in 1965 will have a more cheerful tale to tell than mine. Greatly as I reverence the noble science of mathematical statistics, I do not think even a Newton or an Einstein could solve these problems by force of sheer genius; the biological conditions must be understood; there must be more experimental epidemiology. But he who can conquer the mathematical difficulties will acquire the other necessary knowledge easily enough.

APPENDIX I

The Problem of Intervals

In 1886, W. A. Whitworth published the result which appears in Proposition LI in the fifth edition of his little classic, *Choice and Chance*, viz. that if an event happens at random once in time T the chance that it will not happen in time t is: $e^{-\frac{t/T}{x}}$. Whitworth did not call attention to the fact that Poisson gave this result as the chance that an event would not happen in m trials when its chance of happening was q, if $q \longrightarrow o$, $m \longrightarrow \infty$ and mq was finite, and did not refer to the use of his proposition in studying the frequency distribution of random intervals. He did, however (in the preface to the fifth edition of his book), attach a good deal of importance to another theorem, which he published in a pamphlet in 1898 and is Prop. LVII on p. 208 of his fifth edition. It is this:—

> " If n random magnitudes, α, β, γ . . . be subject only to the condition $a\alpha + b\beta + c\gamma + \ldots = S$ then every term in the expansion of $(a\alpha + b\beta + c\gamma + \ldots)^m$ is of equal expectation, m being a positive integer. And since the number of terms in the expansion is R^n the expectation of each term is S^n/R^n_m
>
> $$\left[\text{where } R^n_m = \binom{m+n-1}{m}\right].$$

* *Op. cit.*, pp. 64–129.

This, as I shall try to show, *is* a more important theorem. So far as I know, no statistician took up the subject until 1915, when L. Von Bortkiewicz contributed a long memoir * to the *Proceedings of the International Statistical Institute* on the distribution of random events in time. This paper is not mentioned in Morant's memoir † (the next contribution to the subject which appeared). Morant's investigation was prompted by some quite crude work of my own which I had mentioned to Professor Karl Pearson, to whom I showed von Bortkiewicz's paper. Professor Pearson did not think von Bortkiewicz had added anything to what Whitworth had done. I did not agree then, and am still of the same opinion; others must judge for themselves; the paper is too long to abstract, I content myself with indicating von Bortkiewicz's line of approach. He began by deducing Whitworth's result (he does not cite Whitworth, whose book he is not very likely to have read—after all, the algebra is very simple, and it would not be surprising if the result were independently discovered over and over again). Von Bortkiewicz wrote the frequency distribution of intervals of length z between successive events, $f(z) = ke^{-kz}$, and obtained the moments of the frequency function. He then took the case of n events occurring in a finite period T. He first completes the number of intervals by supposing that the distances from the origin to the first event and from the last event to T together form an interval. As a first approximation he equates $1/k$ to T/n, subsequently showing that $T/(n+1)$ is a better approximation. Then he takes an arithmetical example, the intervals (in days) between successive deaths of members of the International Statistical Institute in the 13 years 1890–1902. There were 65 deaths, $T = 4{,}747$ days and $T/n = 73{\cdot}03$ giving $k = 0{\cdot}01369$. Here are the results:

Interval	Observed	Expected	Interval	Observed	Expected
0– 35 days ...	25	24·7	140–175 days ...	4·5	3·7
35– 70 „ ...	15	15·4	175–210 „ ...	2·5	2·3
70–105 „ ...	9·5	9·5	Over 210 days ...	3·0/65	3·6/65
105–140 „ ...	5·5	5·8			

Applying the x^2 test to this table (five degrees of freedom) the agreement is rather *too* good ($P = 0{\cdot}98$).

Von Bortkiewicz then shows explicitly that the probability of a events occurring in t is $\frac{(kt)^x e^{-kt}}{x\,!}$ and compares the numbers of deaths in each of the 13 years with the Poisson expectation. As he had only 13 years and the expected number never exceeded 2·28, the comparison is not of value.

There is a good deal more than this in the memoir, but perhaps I have sufficiently illustrated the line of approach.

Morant wrote the function in the form $y_t = \frac{N}{m} e^{-(t-\beta)/m}$, where N is the number of intervals and m and β to be determined. The idea of introducing β was to deal with the case of events which could not be simultaneous (he tested his hypothesis by tapping the key of a chronograph when a random event happened, viz. a 5 appeared in the unit place of columns of four figures read from a census report). This paper is readily accessible, so it need not be abstracted. It contains many interesting results, but those relevant to my problems can, I think, be reached more easily.

I returned to the problem as a relaxation during the " Black-outs " of 1940–2, and started from Whitworth's problem of n points taken at random in a line of length L. Using the proposition quoted above, the mean length of an interval is $\frac{L}{(n+1)}$ and the following results are easily deduced:

$$\left.\begin{array}{ll} \mu_2 = L^2 n/(n+1)^2(n+2)\ddagger & \mu_3 = L^3 2n(n-1)/(n+1)^3(n+2)(n+3) \\ \mu_4 = L^4 3n(3n^2-n+2)/(n+1)^4(n+2)(n+3)(n+4) & \\ \beta_1 = 4(n-1)^2(n+2)/n(n+3)^2 & \beta_2 = 3(n+2)(3n^2-n+2)/n(n+3)(n+4) \end{array}\right\} \quad . \quad . \quad (1)$$

* *Bulletin de l'Institut intern. de Statistique*, 1915, T. xx, 2nd Livr., pp. 30–111.
† *Biometrika*, 1920–1, vol. 13, pp. 309–337.
‡ This, of course, agrees with Morant's *op. cit.* equation (XXVIII) with change of notation.

The Pearsonian type curve with these momental values is (unit area, origin at the start)

$$y = \frac{n}{L}\left(1 - \frac{x}{L}\right)^{n-1}$$

and the area from $x = 0$ to $x = x$ is simply $1 - \left(1 - \frac{x}{L}\right)^{n}$.

The curve passes into the exponential form for n and L tending to infinity, but $\frac{n}{L}$ finite. Indeed, for $L > 100$ and $n > 10$ there is little difference. This is, as Dr. Irwin pointed out to me, not a mere approximation, but an exact solution. The chance that an interval shall exceed x is simply the chance that all n points fall on aggregates of segments adding up to $L - x$, which is $\left(1 - \frac{x}{L}\right)^{n}$, so $dy = -\frac{n}{L}\left(1 - \frac{x}{L}\right)^{n-1} dx$.

So far no practical advance has been made beyond the position already reached by von Bortkewicz. For n small the form is more exact than the exponential, but, as we see, could have been reached in two lines, and if n is small, unless we have a large number of sets of n—say a good many records for families or houses—no comparison of observed and expected intervals is in the least likely to be of use to the practical statistician. But could one not, using Whitworth's theorem, go a stage farther?

It occurred to me that the variance might be a better object of study. The population variance is, as we have seen, $nL^2/(n + 1)^2(n + 2)$, and its range from 0 to $nL^2/(n + 1)^2$.

The variance of the variance can be obtained by the application of Whitworth's theorem, and proves to be $4nL^4/(n + 1)^2(n + 2)^2(n + 3)(n + 4)$. As the range is known, we now have enough information to fit a Pearsonian curve of Type I. Following the usual method,* it appears that $m_1 = (n^2 + n - 6)/4(n + 1)$ and $m_2 = (n - 1)(n + 6)/4$. This is exact in the trivial case $n = 1$, because then $m_2 = 0$ and $m_1 = -0{\cdot}5$, and we shall have equal frequencies for ranges of x from $0 - d^2$, $d^2 - 4d^2$, etc., which must be true since for $n = 1$ the variance is a quadratic function of x. But for n greater than 1 there is no *a priori* reason why the true frequency function should be a Pearsonian type curve at all. After some fruitless attempts to solve the general problem, I consulted Dr. Isserlis who provided me with an elegant solution for $n = 2$.

Taking 0 instead of the mean as origin, the range is from $\frac{L^2}{(n + 1)^2}$ to $\frac{L^2}{n + 1}$, or, taking out the factor $\frac{L^2}{n + 1}$ from $\frac{1}{n + 1}$ to 1. So $Sx^2 = 1$ is the upper limit, and we seek the probability that $Sx^2 = \lambda^2$ for λ^2 between $\frac{1}{n + 1}$ and 1. If $n = 2$, all the representative points must lie in that part of the plane $x_1 + x_2 + x_3 = 1$ bounded by the intercepts on the axes, viz. must be within that portion bounded by the sides of the equilateral traingle formed by joining the points (1,0,0), 0,1,0) and (0,0,1).

In the triangle ABC if D is $(\frac{1}{2},\frac{1}{2},0)$ the equation of CD is

$$\frac{x_1}{\frac{1}{2} - 0} = \frac{x_2}{\frac{1}{2} - 0} = \frac{x_3 - 1}{0 - 1} = k.$$

So at any point C' in CD,

$$x_1 = x_2 = \frac{k}{2} \text{ and } x_3 = 1 - k.$$

If
$$OC' = \lambda,\ \lambda^2 = \tfrac{1}{4}k^2 + \frac{k^2}{4} + (1 - k)^2,$$

or
$$\frac{3k^2}{2} - 2k + 1 = \lambda^2$$

$$(CC')^2 = (\tfrac{1}{2}k)^2 + (\tfrac{1}{2}k)^2 + k^2 = \tfrac{3}{2}k^2$$
$$CC' = k(\tfrac{3}{2})^{\frac{1}{2}}$$

* See, for instance, W. Palin Elderton's *Frequency Curves and Correlation*, 3rd Edition, p. 124.

If G is the centroid of the triangle,

$$CG = \frac{2CD}{3} = (\tfrac{2}{3})^{\frac{1}{2}} \text{ and } GC' = (\tfrac{2}{3})^{\frac{1}{2}} - k(\tfrac{3}{2})^{\frac{1}{2}}.$$

Hence the probability that any representative point fulfils the condition:

$$x_1^2 + x_2^2 + x_3^2 \not> \lambda^2$$

is:
$$\frac{\pi(GC')^2}{\sqrt{\frac{3}{2}}} = \frac{4\pi}{3\sqrt{3}}\left(1 - \frac{3k}{2}\right)^2$$

or — as $\left(1 - \frac{3k}{2}\right) = \frac{3\lambda^2 - 1}{2}$ it follows that $\frac{\pi(GC')^2}{\frac{\sqrt{3}}{2}} = \frac{2\pi}{\sqrt{3}}(\lambda^2 - \tfrac{1}{3})$

provided the whole of the circle falls within the triangle

$$ABC\text{—}i.e.,\ GC' \leq GD,\ k \geq \tfrac{1}{3},\ \tfrac{1}{3} \leq \lambda^2 \leq \tfrac{1}{2}.$$

This can be generalized at once;

for
$$\frac{1}{n+1} \leq \lambda^2 \leq \frac{1}{n}$$

the required probability is:

$$\frac{\left(\lambda^2 - \frac{1}{n+1}\right)^{\frac{n}{2}} \cdot \pi^{\frac{n}{2}} \cdot n!}{\Gamma(n+2)/2 \,.\, (n+1)^{\frac{1}{2}}} \quad \ldots\ldots\ldots\ldots \quad (2)$$

One has merely to write down the volumes of included sphere and including pyramid in space of n dimensions. This means we can write down the probability of values of λ^2 up to $\frac{1}{n}$, which, reverting to the variances, means up to a value of $\frac{n+2}{n^2}$ times the population value. This, for n small, is very useful. If λ^2 is greater than $\frac{1}{2}$ the circle cuts the sides of the triangle and one must subtract from the area of the circle the areas of the three segments so formed, and we now have

$$\frac{2}{\sqrt{3}}(\lambda^2 - \tfrac{1}{3})\left\{\pi - 3\cos^{-1}\left(\frac{1}{\sqrt{6\lambda^2 - 2}}\right) + \frac{3 \,.\, \sqrt{3} \,.\, \sqrt{2\lambda^2 - 1}}{6\lambda^2 - 2}\right\}$$

The generalization of this has not been obtained. A comparison of the results for the exact solution and the Type 1 graduation with $m_1 = 0$ and $m_2 = 2$ for ranges of λ^2 gave the following results:

Range of λ^2	Correct	Type 1	Range of λ^2	Correct	Type 1
0·333 –0·4	0·243	0·271	0·600–0·667	0·074	0·091
0·4 –0·4667	0·243	0·217	0·667–0·733	0·050	0·061
0·4667–0·533	0·206	0·169	0·733–0·800	0·044	0·037
0·533 –0·600	0·113	0·127	0·800–1·00	0·036	0·029

Clearly the Type 1 curve is a mere graduation, although, as often happens with the Pearsonian family, not a bad graduation.

Before Dr. Isserlis gave me his solution, I had made some experiments on random numbers.

The obvious suggestion is to take for L some integer, 50, 100 or whatever is the upper limit of one's patience, and take at random n numbers from 0 to L inclusive, and so form compositions of L into $n + 1$ parts, zero admissible as a part; for instance, suppose $L = 50$ and $n = 3$, and one has taken 3, 7, 25; these give 3, 4, 18, 25 as intervals starting from 0 and ending at 50—viz., a composition. The intervals will be 0, 1, . . . L in length and, writing $n + 1 = r$, there will be r times as many intervals as there are r compositions of L, viz. $r \,.\, (L + r - 1)\,!\,/L\,!\,.\,(r - 1)\,!$, if zero is admissible as a part. The compositions containing 0 at least once will be r times the $(r - 1)$ compositions of L, the compositions containing 1 at least once will be r times the $(r - 1)$ compositions of $(L - 1)$, etc. This is a polynomial of degree $(r - 2)$ and each term enumerates the frequency of occurrence of an interval of 0, 1, 2, etc. For the compositions of L when zero is not admissible as a part are:

$(L-1)!/(L-r)!(r-1)!$ and the frequency of a single zero is $r(L-1)!/(L-r+1)!(r-2)!$, of two zeros $r(r-1)(L-1)!/(L-r+2)!(r-3)!2!$, etc. Multiplying the successive terms by 1, 2, etc., and summing we reach $r(L+r-2)!/L!(r-2)!$ and so on.

In the particular case of $r=4$, the polynomial is $2x^2-2(2L+3)x+2(L+2)(L+1)$. Putting $L=50$ and working out the variance, we have 101·25; the variance for the continuum as given above is 93·75. When $L=100$, the two values are 390 and 375. So L must be very large (and the labour of an experiment very great) to reach a near approximation. It follows that an experiment with L so small as 50 could hardly be expected to give very close results, using the momental values for the continuum, even if the Type I solution of the problem were exact. I did, however, for the sport of the thing, take out from the tables a thousand sets of three numbers,* ranging from 0 to 50 and fitted a Type I curve from the formulæ above deduced. I also fitted a Type I curve from the actual moments of the sample (the mean was actually 98·68, appreciably closer to the value of the polynomial distribution than to the theoretical value). The results are shown in the table.

Range of Variance	Observed	Calculated	Empirical
0– 50	256·5	308·0	282·0
50–100	362·5	298·0	323·0
100–150	196·0	198·0	197·0
150–200	95·0	112·0	106·0
200–250	48·0	54·0	53·0
250–300	29·0	21·0	24·0
300–350	6·0	6·0	10·0
350–	7·0	3·0	5·0
	1,000	1,000	1,000

The fit of the theoretical Type I curve is miserable, owing to wide discrepancies in the first two groups. Isserlis's theorem enables us to check the first subfrequency; it should be 284. It would be special pleading to remark that the mean of the observations being inevitably forced to the right, that would lead to some shift to the right of the subfrequencies, and to note that the subfrequencies above the mean agree quite well with the Type I estimates. To know the truth one must wait until the general problem has been solved, as no doubt it will be, by a better mathematician. Until then, my suggestion is that the Type I approximation for small values of n is probably good enough—using the Isserlis control for the beginning of the range.

In practice, for the kind of problem I had in mind, a serious difficulty arises—viz., that the points cannot be precisely located. We shall be informed that, say, on April 1st m persons fell sick, on April 4th n persons fell sick and can come no nearer to the precise times. If one assumes a random distribution over the 24 hours, one is, *pro tanto*, begging the very question we wish to answer and forcing the data towards randomness; but there is no alternative. Of course, if one has only a single case within a day, and many days intervene between successive cases, the difficulty is trivial. Otherwise it is serious. I have dealt with it in the following way. If m points are taken at random in a line of unit length, the squares of the $(m+1)$ intervals so formed are of equal expectation, and each is equal to $2/(m+1)(m+2)$; we take m times this as the contribution of the first m intervals to the whole sum of squares. The next interval will be between the last point in the first and the first point in the next day with cases. If t blank days intervene, we need $E(x+y+t)^2$, where x is the distance of the mth point from the end of the first day and y the distance of the first of the n points in the next day with points from its start. As the distributions are independent, $E(xy)=Ex\,.\,Ey$. So we have simply: $2(1/(m+1)(m+2)+1/(m+1)(n+1))+2t(1/(m+1)+1/(n+1))+t^2$. Proceeding in this way, we obtain a mean value of the total sum of squares of intervals.

I can see many objections to this plan, but cannot think of a better.

At this point the reader may ask, a little impatiently, whether there is much point in spending

* The expected frequency for any number is 58·82, the range found in the experiments was from 41 to 75 and the χ^2 test (49 degrees of freedom) gave $\chi^2=42{\cdot}4154$ with $P=0{\cdot}52$.

time on tests of a property which is a consequence of an assumption which can itself be tested directly—viz., the assumption that the distribution of cases themselves is rectangular.

We already possess a variety of methods for deciding whether a sample can reasonably be thought to have come from a rectangular parent population (see particularly, Neyman and E. S. Pearson, *Biometrika*, vol. 20A, 1928, pp. 208–21; K. Pearson, *ibid.*, vol. 25, 1933, pp. 379–410; E. S. Pearson, *ibid.*, 30, 1938, pp. 134–48).

I do not think there *is* any logical advantage in using the interval test, but to a medical statistician it has a psychological attraction; he cannot altogether abandon a hope that somehow one might be able to do what Dr. Pickles did—unveil the incubation period of a disease—and it is therefore natural for him to concentrate on the interval between successive events. It may, indeed, be a hopeless quest for two reasons. The first is that the incubation period is not constant. As the table quoted in the text (p. 91) shows, in the experimental inoculations there is a wide scatter around the mean interval. In the next place, the time during which a patient is capable of passing on infective material to somebody else may be long. The purely arithmetical problem is complex. To solve it will need both more analytical skill and more data than I command.

I am very grateful to Dr. L. Isserlis, Dr. J. O. Irwin, Dr. W. J. Martin and Mr. M. G. Kendall for their help and advice in this work.

APPENDIX 2

Brownlee's Epidemic Frequencies

The earliest of Brownlee's mathematical papers on this subject appeared in *Proc. Roy. Soc. Edin.* June 18th, 1906, pp. 484–521, the latest in *Proc. Roy. Soc. Med. Sect. Epidem. and State Med.* 1918, pp. 85–127. This note is based on the latter. I have retained the author's notation and method of deduction, even when they seemed capable of improvement.

Brownlee, like Karl Pearson, based his system on the limiting ratio of successive ordinates; his y_t is the number of new cases (or deaths)—viz., the number of newly infected persons (or of deaths) at time t; his x_t the integral of y from the origin to time t. In his terminology infectivity is the ratio of successive ordinates. He proceeds by expanding the right hand side of

$$\frac{y + \Delta y}{y} = [\phi(t,y)]$$

giving

$$\frac{\Delta y}{y} = \log [\phi(t,y)]\Delta t + [\log \phi(t,y)]^2 \frac{(\Delta)y^2}{21} + \ldots$$

and so has for his fundamental form:

$$1/y \,.\, dy/dt = \log \phi(t,y) \quad \ldots\ldots\ldots \quad (1)$$

If the infectivity decreases geometrically—viz., is equal to e^{p-qt} then

$$\frac{1}{y} \cdot \frac{dy}{dt} = p - qt \quad \ldots\ldots\ldots \quad (2)$$

and

$$y = c \,.\, e^{pt - \frac{1}{2}qt^2} \quad \ldots\ldots\ldots \quad (3)$$

the Normal Curve. Perhaps some readers may feel a difficulty which Brownlee endeavours to remove in the following words:

> " The method as developed apparently requires that the incubation period of the disease should be infinitesimal, which, of course, never occurs in practice. This, however, is not necessary in all cases."

Brownlee remarks that this form implies that the rate of increase is directly proportional to the number of new cases occurring at that moment, and introduces a power of y as a factor putting

the infectivity equal to $e^{y^n(p-qt)}$. He always attached great importance to Farr's view that the death rate was proportional to a power of the density of population.

If
$$\frac{1}{y}\cdot\frac{dy}{dt} = y^n(p - qt)$$
$$y = n(c - pt + \tfrac{1}{2}qt^2)^{-1/n} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Which by change of origin reduces to the symmetrical case of the Pearsonian Type IV, sometimes numbered Type VII.
$$y = \frac{M}{(1 + t^2/a^2)^m} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Should n be negative (*e.g.*, partial immunization through non-clinical, unrecognizable attacks of the disease, might reduce liability) we should reach a Pearsonian Type II:
$$y = M(1 - t^2/a^2)^m \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The tacit assumption has been that the number of persons attacked in the whole epidemic is so small a fraction of the exposed to risk that the supply of victims is virtually constant. If the infectivity is constant, the population P and x the number of victims from $t = 0$ to $t = t$, then:
$$\frac{1}{y}\cdot\frac{dy}{dt} = \log k(1 - x/P) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

This cannot be integrated to give y explicitly as a function of t, but a solution can be obtained indirectly (see *op. cit.*, pp. 121–2), and Brownlee tabulated results for infectivities from 1·2 to 2·6 per unit of time and gave the β's, σ's and percentages still unaffected at the end of the epidemic. He also suggested a modification to allow of population increase or decrease—viz.:
$$\frac{1}{y}\cdot\frac{dy}{dt} = kf(x)(P + pt - x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Except in the particular case of $f(x) = x$ (which had been considered by Ross), Brownlee goes no farther with this. Returning to (3), he considered the effect of allowing for an increase or decrease of infectivity, which could be effected by, *inter alia*, multiplying e^{p-qt} with $(a + bt)$ giving
$$\frac{1}{y}\cdot\frac{dy}{yt} = \log(a + bt) + (p - qt)$$
$$y = C(a + bt)^{a/b + t}e^{(p-1)t - \frac{1}{2}qt^2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Brownlee comments:

> "This curve is asymmetrical and the descent of the epidemic is more rapid than the rise. This means that the maximum of the epidemic occurs later and as the infectivity is largely lost by this time the descent is rapid. Similarly it may be found by applying a factor $1/(a + bt)$ that when some progressively inhibiting influence is at work the form of the epidemic is so changed that the decline of the epidemic is less rapid than the rise. Such factors must be considered where the influence of such a condition as varying temperature on the progress of an epidemic is examined, a subject as yet hardly worked at. It may be noted that in the case of the normal curve an exponential increasing or inhibiting factor alters the position of the maximum without changing the form of the epidemic."

Discussion on Professor Greenwood's Paper

Mr. M. G. Kendall: I move the vote of thanks to Professor Greenwood with great pleasure. He has done us a service in reviewing the relationship between the medical and statistical approach to epidemiology, but I cannot help feeling somewhat on the defensive. My difficulties begin with the remark that "Hirsch was not a stupid man, but his criteria were really statistical," the operative word being "but." This is the sort of epitaph which many people would like to write on our graves, and Professor Greenwood has raised in the epidemiological field a question which deserves to be debated at some length. Should research on epidemiology be done by a medical man who has learnt statistics or by a statistician who has learnt medicine? To take an even more con-

tentious case, who does the best research in economic statistics, the economist who has learnt statistics or the statistician who has learnt economics?

What the answer is I do not know, but I suspect that there is no answer, and that ultimately it makes no difference if the man concerned is sensible. I fully agree with Professor Greenwood in his view that the mathematical statistician is likely to go badly astray unless he understands the subject with which he is dealing. I hope he agrees with me that it is not necessary to have a detailed medical knowledge in order that a statistician may make useful contributions to epidemiology. If so, we are in complete accord and can join forces against the protectionist fallacy that only an economist should be allowed to handle economic statistics.

What, then, are the main directions in which a statistician can contribute to epidemiology? I should have said that there were three:—

(*a*) In the first place the statistician can help to ensure that the data are representative. There are peculiar difficulties in sampling for medical studies, particularly among human populations, and in no branch of science is it more necessary to call in expert statistical advice at the outset of an enquiry.

(*b*) Secondly, the statistician can indicate what sort of information is required for the solution of a problem. Professor Greenwood has given an illustration in the very interesting tables exhibiting the periods of incubation of infantile paralysis. Distributions such as this are, I think, essential for an adequate discussion of epidemics, and I hope that many others will be produced, if only for the benefit of parents like myself, who never quite know how long it is likely to be before children can be regarded as clear of infection from measles or mumps, and spend most of their earlier married lives in a state of suppressed incubation.

(*c*) Thirdly, the mathematical statistician can often throw light on a medical problem from his experience in other fields. This brings us to the problem dealt with by Professor Greenwood in his Appendix A.

As he says, it was Whitworth who seems to have been the first to consider this problem in any sort of generality, but it may be of interest to point out (what is not generally realized) that the essential mathematics of Whitworth's theorem were carried out by Dirichlet earlier in the nineteenth century. Whitworth himself proves his result by a long inductive chain of argument, whereas it follows almost immediately from Dirichlet's integrals.

More recently the problem has been studied from the point of view of finding the distribution of the greatest part into which the magnitude is divided. Whitworth himself solved this problem, but it has been re-discovered and applied, for example, by Fisher to harmonic analysis, by several writers to the test of significance of the variance-ratio in the analysis of variance, and by Garwood and others in problems arising out of the control of traffic and telephone switchboards. More recently still Stevens solved what is essentially the same problem in connection with the distribution of points on a circle, a form which I think was suggested by biological considerations.

Nearly all this work has concerned the distribution of the *greatest* of the fragments into which the random interval is divided. Professor Greenwood has, however, put forward rather a different form of the problem, since he is more interested in the closeness of equality of the parts, and he has accordingly suggested as a test of departure from randomness the distribution of the variance of the parts into which the interval is divided. I do not remember seeing this version before.

The general distribution required by Professor Greenwood as a generalization of Dr. Isserlis's result is equivalent to finding the volumes cut off by hyperspheres in u dimensions on a hyper-tetrahedron. The problem proposed is not insoluble, but it makes a very considerable call on one's powers of geometrical insight. In the time available I have not been able to make any progress with it. There are, however, several other ways of tackling the problem, and I will briefly mention six by way of illustration of the resources at our disposal.

(*a*) Professor Greenwood has fitted a Pearson curve to the distribution by using the first two moments and the range. I think a better fit would be obtained if one used the first four moments and ignored the range. In many of these cases it is better to identify lower moments and to leave the range to look after itself, and I should expect by so doing to get a better fit, at least as regards areas under the curve, which are the main objects of enquiry in this connection.

(*b*) It might be worth while examining the possibility of finding a fit to the distribution function rather than to the frequency function. It appears that for small values of u the distribution is unsymmetrical, and close fits near the start of the curve are likely to be rather difficult to obtain. The cumulative frequency function or distribution function is likely to be a good deal smoother, and therefore more amenable to fitting.

(*c*) It is possible that a transformation of the variate might bring the distribution closer to symmetry or normality, and hence provide a better fit.

(*d*) Although in general the variance is a more convenient measure of dispersion, this particular problem might be mathematically more tractable if one worked with the mean

deviation. The geometry of the sampling distribution would be complicated by changes of sign in the various quadrants, but at any rate the volumes cut off would be bounded by planes and not by spheres.

(*e*) Another possible measure to test the departure of the parts of the interval from equality would be the difference of the greatest and the least parts, or the ratio of the greatest to the least. I should expect the latter to be quite a sensitive index for the purpose, and the distribution theory might be a good deal simpler than for the variance or the mean deviation.

(*f*) Finally, some sort of test might be obtained by examining the correlation between successive intervals. If the division of the magnitude is random, one would expect zero correlations within sampling limits, but if the division is regular, positive correlations might appear, although in practice no doubt the situation would be complicated by the variation in incubation periods.

DR. FRASER ROBERTS: I am sure that Professor Greenwood must be accustomed to being thanked, not only for very valuable papers, but for his great gift of making everything he describes so interesting. In the course of his paper Professor Greenwood mentioned the difference in the incidence of infantile paralysis amongst officers and amongst other ranks in the Army in India during the war. I wonder whether he would apply the same explanation to the similar difference found in the Navy in the incidence of infective jaundice. Throughout the entire Navy the incidence of jaundice was considerably higher among the officers than among the ratings. The same thing was true in the Army and Air Force—particularly, I believe, in the Army in the Middle East.

I am afraid that I am not qualified to take part in the mathematical discussion, although I shall listen to it with great interest. I feel guilty in many ways because I should have taken much more interest in epidemiology at an earlier age. My own native town contains a remarkable, a unique, monument, not, indeed, to an epidemiologist, but to a man who struggled with a particular epidemic of cholera about 100 years ago. He was a doctor who was renowned for his eccentricity as well as for his courage. He attended his patients during that epidemic, he refused to leave them, and when they died they were buried by another local eccentric who also refused to leave the place.

The epidemic passed, and the grateful townsfolk desired to raise a memorial fund. They suggested scholarships for local boys, but the doctor said he would much prefer to have opposite his house a very tall column with a statue of himself on the top. In spite, I regret to say, of a very handsome donation from the doctor himself, the fund did not quite run to it, and so what was clearly regarded as the least essential detail had to be left out. However, there now arises in this town in a small public garden an enormous column 40 or 50 feet high, and on the top of it is a statue, not of the worthy doctor himself but a second-hand one of Lord Palmerston—whom I believe the doctor did somewhat resemble!

The vote of thanks was then put to the meeting and carried unanimously.

DR. J. A. SCOTT said that it was a great pleasure for him, as a medical officer of health who was not a statistician, to pay his tribute of admiration to Professor Greenwood. In the early part of his paper Professor Greenwood had mentioned that continued growth was not "epidemic" beyond middle life, but in so far as mental growth was concerned he thought Professor Greenwood would have to modify his observation in relation to people who had the benefit of contact with his mind and thought. A medical officer of health had some sympathy with the observations made by the proposer of the vote of thanks on the question of which came first, the hen or the egg—in other words, the doctor or the statistician. In a field like medicine, in which qualification took a very long time, a combination of those qualities was rarely found. It was of some interest that Professor Greenwood was probably only the fourth of the very few medical statisticians concerned with epidemiology in this country. He had mentioned three of them—namely, Farr, Brownlee and Ross—and the speaker thought that no one had intervened between these three and Professor Greenwood himself.

Probably from the point of view of knowledge of the statistical side of epidemiology the only possible workaday arrangement would be some liaison between the epidemiologist-qua-medical man and the statistician-qua-statistician. He was particularly interested in Dr. Pickle's observations on the incubation period of epidemic catarrhal jaundice. This took his mind back to 1937, when he was medical officer of health for Fulham and had an interesting experience of the same disease. In a day nursery an epidemic originated from a probationer nurse of 18 who had scarlet fever. She was in hospital for four months, and while in hospital had an attack of jaundice. She was discharged on April 3rd, and had a fortnight's sick leave, coming back to the nursery on April 13th. She shared a bedroom with four other nurses. On May 6th one of these nurses fell ill, and on May 10th showed signs of jaundice. On May 9th two other probationer nurses felt unwell and subsequently got jaundice. A fourth nurse a few hours later started the same cycle, jaundice being marked on May 14th. From the first development of the illness to the actual exhibition of jaundice two or three days elapsed. But within a month of this probationer nurse coming back to the nursery four nurses sharing the same bedroom went down with the complaint.

There was a great deal of this kind of statistical information available to the medical officer of health on which the statistician could work. How the medical officer and the statistician were to work together he was not quite clear. He himself had had forty children under the age of 5 in this day nursery. The nurses were with them all day long. Two or three of those children, during the time this probationer nurse was affected, had mild attacks of vomiting with bile salts in their urine, but not a single one had jaundice. That seemed to underline the need for a liaison between the medical officer and the non-medical statistician. The only criterion of epidemic catarrhal jaundice could not be jaundice alone, any more than in infantile paralysis could it be paralysis alone, for with every case of paralysis there were four or five others which had a related illness, but not infantile paralysis.

Between the statistician and the medical man, the epidemiologist was essential if much progress was to be made in working out all the biological laws underlying epidemiology. From one's own routine experience one could bring forward similar instances in connection with measles. In his borough measles was a notifiable disease. In London and in some other places measles occurred in biennial epidemic waves, and it was of some interest to him to examine the incidence of measles in children under 5 who were attending school and children under 5 who were not. He started with the theory that there was a bigger risk of infection among the children attending school and mixing with other children, and he had the opportunity of working out a few figures which did satisfy him that there was a greater liability during an epidemic period for a school child under the age of 5 to have measles than a child of similar age who did not go to school.

Material of that kind was available, but was not utilized as it should be by the statistician. It would certainly throw a little more light on biological phenomena, and he personally would plead for some further co-operation and team work between the statistician and the medical officer. How that team work should be done was not for him to say. The medical officer was usually frightened out of his wits by the controls and requirements of the statistician, but it should be possible in large towns to have a statistician in the department of the medical officer of health. Certainly such statisticians would be very useful in view of the future development of the hospital services which was looming ahead. In the smaller towns the work might be done through the regional university. In that way more use could be made of the material which was available.

One final observation on Professor Greenwood's mathematics. As a field worker it all passed over his admiring and non-comprehending head, but it was very pleasant to see it on paper, and he hoped that Professor Greenwood and his successors would have an opportunity of applying it more fully to the material which medical officers of health possessed.

DR. MELVILLE MACKENZIE expressed his deep appreciation of Professor Greenwood's paper, not only from the point of view of its own merits, but because of the offer which it made of co-operation. He was quite convinced that in many fields of epidemiological enquiry there should be a much closer contact with statisticians and at an earlier stage. Many medical officers investigating epidemics had very little idea of what material was likely to be of use to statisticians, and it would be a great step forward if they could be informed in some detail as to the type of material which could be utilized. In much of the work, of course, they were concerned primarily with stopping the disease, but in a certain number of enquiries they did undertake work entirely from the research point of view. One of these was anterior poliomyelitis, in which little could be done for prevention, and such enquiries as were carried out were by way of research. At the same time, one had to admit that it was impossible to get down to an enquiry with a cut-and-dried scheme. Factors and conditions varied enormously, but if a general guide could be laid down it would be of great help to the Ministry of Health, which would be most happy to collaborate in any way which Professor Greenwood might suggest.

He had been very much pleased also to hear Professor Greenwood's plea for further research generally in epidemiology. He believed that during the war the public learned a very great deal about the value of research in the progress of the war, and that at present the public were ready to spend money on research, as they had not been before the war. The Ministry of Health and the Public Health Laboratory Service looked forward to carrying out a considerably increased amount of work during the next few years. Concerning the controversial question of statisticians *versus* doctors, it seemed to him that the only way in such a field as anterior poliomyelitis was to have the clinician, the statistician and the field epidemiologist all working together.

He desired to say a word about influenza. He had just come back from Austria and Germany, where the conditions from the epidemiological point of view were perfect for the spread of influenza and for a high mortality rate. But in actual practice in the British zone there had been relatively few cases of influenza and absolutely few deaths. That raised another point on which possibly Professor Greenwood might be able to help them statistically—namely, the question whether under-nourishment did make for the spread of epidemics or not; in other words, whether the under-nourished were more easily infected in the first instance, and whether, having been infected, they died more frequently. Most of them would say that epidemics spread more easily in a badly nourished population, but the question was constantly recurring as to whether there was a great

danger of epidemics in an ill-nourished community. He had had occasion to search for any authoritative statement in support of the idea that bigger rations would prevent epidemics, but there was not much scientific support for such a statement. The question was of great importance. Actually the great pandemic of influenza in 1918 and 1919 occurred amongst the well-nourished and younger portion of the community. He believed also that under-nourished monkeys could not easily be infected with anterior poliomyelitis, and that hedgehogs under-nourished could not be infected with foot-and-mouth disease. This made it all very difficult.

Concerning poliomyelitis from a statistical angle, this was an unfortunate theme to discuss. From the epidemiological point of view they were completely lost in the disease. They knew that there were precocious carriers—people who had the virus in their stools before they developed the disease—but there were also ordinary carriers—convalescents and others—and there were certainly many persons who had mild attacks which were not regarded as poliomyelitis at all. The number of cases of anterior poliomyelitis which occurred in the north midland region during the six years of war was 231. These cases were spread amongst sixty-eight local authorities; seventy of them occurred in the area of five local authorities. Therefore they were scattered in ones and twos throughout the entire area. This made investigation exceedingly difficult. One other point about anterior poliomyelitis from a statistical angle. In a recent outbreak in a boys' camp there were nine cases, eight out of the nine had had while in camp some form of transient illness, one did not develop drowsiness until ten days after a second attack. Of the thirty boys who did not get the illness six had a transient attack. One boy had a similar second attack with stiffness in the back and neck which would never have been spotted had not the practitioner attending the case been aware of the occurrence of the epidemic. This boy ten days afterwards had a similar clinical attack with extensive paralysis.

The other point he desired to mention was in connection with a recent visit to the United States, where he had been very much struck by the extensive use made not only of statistics in epidemiology, but also with the interest of the community in disease, both in terms of death-rate and incapacity to work. At every stage the capacity to work was determined by statistical examination. There was quite a considerable need for the further use of statistics in this country in these investigations.

In thanking Professor Greenwood, he again promised the willingness of the Ministry of Health to help him in any way possible.

DR. IRWIN said there were two reasons why he could speak on this paper with a certain propriety, apart from the fact that it gave him great pleasure to do so. First the subject was one in which his interest went back about twenty years.

When he was a young man on Professor Karl Pearson's staff, he tried to tackle the problem of predicting the course of an epidemic from a knowledge of some weeks of initial cases. He assumed the form would be adequately described by one of Pearson's Types, and used the method of moments. He failed, as Professor Pearson had done before him. The reason might have been because the hypothesis of a Pearsonian form of distribution was wrong, or because in fitting the tail of a distribution which, considered in itself, was naturally a very skew curve, the method of moments, which he tried, was a very inefficient method of fitting.

He supposed he was one of the few people, if indeed they were few, who read Professor Greenwood's 1931 paper on chain binomials. Indeed, he well remembered feeling honoured at being asked to give advice on it, shortly after joining Professor Greenwood's staff, one of the first duties which he had to perform. Later he became interested in Kermack and McKendrick's theoretical studies, and in particular their application to some of Greenwood and Topley's data on mouse ectromelia and mouse typhoid. He still thought, if it was not presumptuous to say so, that more might be done on those lines.

However, he supposed that he would be expected to say something on the problem considered in Appendix 1.

He had to thank Professor Greenwood for giving him some happy hours in trying to solve it, and it might be worth while stating what he did. He obtained the solution—that is, the distribution of the variance of the intervals, for 2 and 3 intervals, the latter by a method which involved calculating the area common to an ellipse and a right-angled triangle, and verified that the variances of the distributions so obtained agreed with those calculated directly. Later he saw that Isserlis's method, which involves calculating the area common to a circle and a symmetrically placed equilateral triangle, would be the easier to generalize, and obtained, as Dr. Isserlis did, the distribution of the variance for any number of intervals and sufficiently small values of the variance. The problem of four intervals involves the volume common to a regular tetrahedron and a symmetrically placed sphere, and there is some difficulty in the case when the sphere cuts the edges as well as the faces of the tetrahedron. In the case of three intervals the distribution of the variance is shaped rather like a Wellington boot. It is rectangular for $0 \leq v \leq \frac{L^2}{18}$, and the frequency then declines to zero at $v = \frac{2L^2}{9}$. The tangent has one point of discontinuity. For four intervals the curve rises

to a mode, and there are two points at which the analytical form changes. For a number of intervals $(n+1) \geq 4$ there is of course a mode, and there are $(n-1)$ points at which there is an analytical change of form. He (the speaker) obtained the distribution of the variance for two and three intervals in a form which was rather more explicit than that given by Professor Greenwood, and this seems worth putting on record. The period of exposure to risk being unity, the interval length being x and defining the variance of the $(n+1)$ intervals determined by n cases by

$$v = \frac{1}{(n+1)} \Sigma \left(x - \frac{1}{n+1}\right)^2$$

the distribution of v is:

for $n+1=2$ $\qquad \frac{dv}{v^{\frac{1}{2}}} \qquad 0 \leq v \leq \frac{1}{4}$

for $n+1=3$ $\qquad 2\sqrt{(3)}\pi dv \qquad 0 \leq v \leq \frac{1}{18}$

$$\left[2\sqrt{3}\pi - 6\sqrt{3}\cos^{-1}\left\{\frac{1}{\sqrt{(18v)}}\right\}\right]dv \;.\; \tfrac{1}{18} \leq v \leq \tfrac{2}{9}$$

Both Mr. Eliezer, a pupil of his at Cambridge, and he spent some time in trying to get the complete generalization for $(n+1)$ intervals, but were not successful. Someone with Professor Fisher's geometrical intuition seemed required.

If one confined one's attention to the total period between the first and last cases one could, on the hypothesis tested, regard the resulting $(n-1)$ intervals as a random sample of $(n-1)$ values from an exponential distribution and the variance $\frac{1}{(n-1)}\Sigma\left(x - \frac{1}{n-1}\right)^2$ would have a distribution of the same form as before. Dr. M. S. Bartlett had pointed out to him that the variance was not necessarily the best measure of heterogeneity in the sense of departure from the exponential form, and had suggested another whose distributional properties might be easier to determine.

Finally Dr. Irwin would like to say that during the war he did not see as much of his old chief's writings as he had done previously, and it was a real pleasure to read this paper through and to find that the war, which was wearing for them all, had changed neither the profound learning nor the literary fascination of his style. As an illustration of the latter he would like to read a quotation from each of two authors.

Dr. Irwin then read Macaulay's description of the pestilence among Schomberg's troops in Ireland (*History of England*, Vol. II, Chap. XIV, p. 539, in the Everyman edition) and Greenwood's description of plague in India (*Epidemics and Crowd Diseases*, p. 297). He concluded by saying that Professor Greenwood's style combined with the accuracy of the statistician all the picturesqueness of Macaulay.

Dr. M. S. Bartlett desired to amplify by a word or two the suggestion he had made to Dr. Irwin on the problem set in Appendix 1 concerning random intervals following an exponential distribution. This distribution was itself a distribution of a variance with two degrees of freedom from a normal sample, and therefore the problem was identical with testing homogeneity or heterogeneity of a set of such variances. A test was immediately available if one regarded it from that point of view.

The χ^2 method which he had proposed * for making this test was not too good an approximation if, as here, the degrees of freedom per variance were only two, but other writers † had investigated this particular case in more detail with a view to getting more precise significance levels.

Mr. P. A. Moran said that at the suggestion of Mr. M. G. Kendall, he had been studying the distribution of the sum of the squares of the intervals formed by the random division of a line. This was equivalent to considering the volume common to an n-dimensional sphere and an n-dimensional regular simplex of the same centre. The calculation of the exact distribution would be extremely awkward. It was, however, possible to express the result for n-dimensions in terms of that for $n-1$ dimensions. It was also possible to calculate the lower moments by using Dirichlet's integral. Moreover, by using a new type of non-linear Central Limit Theorem it was possible to show that the distribution tended to normality for large n. He hoped to publish these results shortly.

Mr. Mason said it was not clear from the discussion of Aycock and Eaton's infantile paralysis results whether it was their view or Professor Greenwood's that " none of the secondary cases with intervals not exceeding six days could have been derived from the primary cases, and that the patients must have been infected in some other way." This assumption was not logically acceptable.

* *Proc. Roy. Soc.*, A, **160** (1937), 268.

† See, for example, Bishop, D. G., and Nair, U. S., *J.R.S.S. Suppl.*, **6** (1939), 89.

unless the period of incubation could be shown to be the same as that before infection was transmissible. He felt infection *could* take place before incubation was complete or diagnosed, so that it was quite possible for a case in the " interval 5 " or even " interval 1 " column of the table to be related to one in the " 0 " column. Thus the interval in days for this purpose should be reckoned from some earlier time x from which the infection might start. These possibilities should, therefore, he felt, be exhausted first.

PROFESSOR GREENWOOD, in reply: I am very grateful for the generosity with which my friends and colleagues have treated this paper. On the mathematical side, I shall profit from the suggestions and comments of Mr. Kendall, Dr. Irwin, Mr. Moran and Dr. Bartlett. I mean I shall profit personally; to the amateur it is delightful to wander in the mathematical paradise; in doing algebra—often quite ineffectively—I almost forgot the *Blitz* which was in full swing when most of this paper was written. Of course the problem will be solved, if it is worth solving, not by me but by one of the speakers. My concentration on the variance was partly mere tradition, partly a notion that as, in practice, the samples would be very small, the variance was likely to be the most useful measure. On the epidemiological side I am equally grateful. I think Mr. Mason is right that the tacit assumption I made and, I think but am not quite sure, Haycock and Eaton made, that an infected person cannot convey the disease during the incubation period is arbitrary. I shall try to investigate the point. I wish to emphasize what Dr. Scott and Dr. Mackenzie said of the importance of data which are not used, really because those in possession of them have other, more urgent, tasks to perform. I have reserved to the end of my reply the first point raised in the discussion—viz., should statistical research in epidemiology be done by a medical man who has learnt statistics or by a statistician who has learnt medicine. I have deliberately restricted the generality of Mr. Kendall's question by introducing the adjective "statistical," because I think other speakers have made it clear that study in the field can be done only by medical men, and by medical men who have had experience wider than that an undergraduate training in a medical school provides. Even so limited, the question is hard to answer.

I think this paper and the comment upon it bring out the bad and the good points of the kind of work done by a person whose upbringing has been fundamentally medical, whose mathematical knowledge, such as it is, has been largely self-taught.

The bad points are obvious enough. Having posed my mathematical-statistical problem, my handling of it has been unskilful because I had neither the knowledge nor the facility (which comes only from long training) to switch over to an alternative approach, but stolidly proceeded with a frontal attack on old-fashioned lines. That is the incurable weakness of the amateur. On the good side, an interest in the problem for its own sake, an appreciation of its biological importance and, perhaps, even memories of visiting sick people in the East End of London when I was my father's assistant more than forty years ago, may, perhaps, have enabled me to bring the data more vividly before a casual reader, than a mathematical statistician could have done.

Perhaps there is some analogy between the situation I am considering and that of the legal profession. The primarily medical statistician is the solicitor, the primarily mathematical statistician the Chancery counsel. The solicitor *must* know enough law not to lead his client to disaster, the more law he knows the better, but, above all, he should know human beings.

I cannot answer Mr. Kendall's question decisively. I am sure that some men whose primary training has been statistical can acquire a great deal of medical knowledge: I can think of conspicuous instances. I know how difficult it is to acquire fundamental mathematical knowledge after undergraduate age. On the whole, speaking statistically, I think the medical experience should come first, but I should be sorry to see a barrier erected.

As a result of the ballot taken during the meeting, the candidates named below were elected Fellows of the Society:—

Walter George Bailey, F.I.A.
Reginald Francis Hugh Banister, B.Sc.
Marcus Bridger.
Sydney Cyril Boxer, B.Sc. (Econ.)
John Peter Burman.
Dudley Albert Clark, B.A. (Econ.)
James Alfred Cornell.
Rudolph Dalberg, Dr. phil., Dr. jur.
Edward Thomas George Emery.
Vernon Eric Gough.
John Baur Greenwood.
Phyllis Ann George.
Stanley Richard Harvey.
Alec Richard Holmes, B.Sc. (Econ.)
Arthur Howarth, M.Sc.
Lieut-Col. R. D. H. Jones.
Thomas Herbert Kelly.
Per Kirstein.
Elsie Anna Grace Knowles.
Derrick Norman Lawley.
Anthony Herbert Leppard.
Walter Levy, B.Sc. (Econ.)
George Osborne McLean.
John Hylton Madge.
Bernhard John Albert Martin.
John Mars, M.A., M.Com., B.Litt.
Irena Mathison.
Gomer Hanworth Morris.
Alfred Stephen Musk, F.I.A.
Philip Edward Naylor.

Percival Albert Outridge, B.Sc., F.I.A.
Harry Pratt.
Andrew Bandi Reisz.
Campbell Secord.
Edmund Fleetwood Sheppard.
Reza Shimy, B.Sc.
Edward Hugh Simpson, B.Sc.
Edwin Frederick Winchester Sumner, F.I.A.
Thomas Ronald Suttie, F.I.A.
Agnes Teleky, Ph.D.
Major Maurice Arthur Warneford Vale.
Julia Rule Weatherburn.
Leslie Thomas Wilkins.
Thomas Wilson.

Corporate representatives.

Malcolm Alexander Campbell Macneill, *representing* the Anglo-Iranian Oil Company, Ltd.
Walter Taplin, *representing* The Economist Newspaper.