THE RELATION BETWEEN PUERPERAL SEPTICAEMIA AND CERTAIN INFECTIOUS DISEASES.

By PETER L. McKINLAY, M.D., D.P.H.
(*National Institute for Medical Research, Hampstead.*)

(With 3 Diagrams.)

The possibility that the prevalence of diseases in which there is no specific causal organism may be affected by the prevalence of other diseases of a contagious nature is well recognised. Even in the early days of bacteriology interrelationships between infectious diseases and puerperal septicaemia were suspected on purely statistical grounds. Longstaff (1891), for example, pointed out the remarkably close correlation between the seasonal variations and the secular trends of the mortalities of erysipelas and childbed fever—a relationship so close that he "found it difficult to avoid the conclusion that they were both due to the one poison." A somewhat similar but less striking association was shown with other inflammatory diseases, such as pyaemia, scarlet fever, "rheumatism of the heart or pericardium" and diphtheria. Even more emphatic were the views of Minor (quoted by Longstaff) who, with reference to the association between erysipelas and puerperal fever, gave reasons for the belief that there existed an intimate connection between them, and that "in any place where erysipelas is found, there will be found puerperal fever." Further, on examining the alleged connection of typhus fever and scarlatina with childbed fever, Minor concluded that: "1. Epidemic typhus is *not always* associated with an outbreak of epidemic childbed fever. 2. Epidemic scarlet fever is *very seldom* associated with an outbreak of childbed fever. 3. Epidemic erysipelas is *invariably* associated with an outbreak of childbed fever." Geddes (1912 and 1926), in two contributions to the study of puerperal sepsis, has also examined the suspected relationship between three epidemic infectious diseases and the varying prevalence of puerperal fever. His results would appear to show that the correlation is closest with erysipelas, somewhat less with scarlet fever, whereas diphtheria shows no close affinity with the incidence of puerperal fever. The author, however, appears to place little importance on the result, regarding it as a subsidiary consideration compared with his main (statistically unproven) thesis as to the factor of greatest importance in determining the prevalence of septic infection in puerperal women.

With advancing knowledge of bacteriology and with increasing indications of the relationships in clinically different diseases between their causal agents, not only in their morphology, but also in cultural characteristics and in the specific morbid effects on their injection into animals, some at least of these relationships would appear to have an even greater significance than, for example, the explanation suggested by Longstaff, namely, the prevalence of rainfall or the number of rainy days acting by purifying the air and removing from it particles of contagious matter and making them less diffusible.

In puerperal fever, as in other inflammatory conditions, bacteriological findings indicate that there is in all probability no specific organism, but "if general infection ensues, usually one organism only invades the blood stream, and this is almost always the streptococcus" (Lea, 1910); and it is apparently agreed that *streptococcus pyogenes* is the most common infecting agent in at least the severe types of childbed fever. The bacteriological reports of different investigators vary somewhat in the proportion of cases in which the streptococcus has been isolated. The reports of the London and North of England Committees on puerperal sepsis (1925) deal only with blood examination. In the former investigation it was found that in 53 of the 136 cases examined there were streptococci in the blood, 4 had *B. Coli* and in the remaining 79 instances the blood examination proved negative. In the North of England Committee's report, 65 per cent. of the 75 cases examined gave positive streptococcal cultures. Colebrook (1926) believes that a haemolytic streptococcus is responsible for about 90 per cent. of all cases of puerperal septicaemia. Similar results are quoted by other investigators. Mackay (quoted by Furneaux Jordan, 1912) found a streptococcus in 17 out of 21 cases. This organism, he considers, is quite distinct from other streptococci, is the same identically in all the 17 cases, and that in any secondary pus, pleuritic fluid or sputum, it is identical with that found in the uterine discharge. Further, he has never seen a streptococcus with similar characteristics in any other type of sepsis. Bigger and Fitzgibbon (1925) in 158 swabs found streptococci present in 101 instances, and Abrahams (1924) isolated streptococci in 63 out of 120 swabs. The controversy concerning the characters of the organism with regard to its cultural characteristics, fermentation reactions, etc., and the original source of the organism does not affect this study in any way. Sufficient it is that one of the chief causal agents in puerperal septicaemia is *a* streptococcus, and we are concerned here with the effect of the incidence of other diseases due to, or intimately associated with streptococci on the prevalence of septic infection in puerperal women.

In erysipelas the causative organism, *streptococcus erysipelatis*, was isolated by Fehleisen in 1884, and this organism, on inoculation in the human subject as a therapeutic measure in malignant disease, reproduced erysipelas. But although erysipelas remains true to type, in view of the fact that many of the other supposed differences have been eliminated, the general belief now is that the streptococcus of erysipelas is simply a pyogenic streptococcus of modified virulence.

In scarlet fever, recent bacteriological researches seem to have established an etiological relationship with a streptococcus. Whether this organism is the *causa vera* of the condition or a mere associate has no concern for us here.

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Certain it is that a streptococcus is almost constantly present in at least the superficial lesions, although scarlatinal joint effusions and renal complications in many instances have proved sterile.

That the association of puerperal women with patients suffering from certain infectious diseases is still regarded by medical authorities as a potential source of infection in the puerperium may be inferred from the report on two cases (investigated by the North of England Committee) in which the infection is supposed to have been conveyed from another patient. In one of these a patient in the next bed was found to be suffering from scarlatina; in the other, the woman's husband developed erysipelas of the face and was transferred to a fever hospital. This misfortune so upset his wife that labour started prematurely, and the child was born before the arrival of either doctor or nurse. This patient developed septicaemia, in spite of the fact that everything was normal at the confinement, and there was no vaginal examination.

The investigation of the possibility of a direct relationship between these differently situated inflammatory conditions, as opposed to an indirect correlation by the intermediary of some general prevailing cause such as rainfall, seems therefore to be of some importance. The question to be answered is not whether, when there is close contact between a puerperal woman and a patient suffering from infectious disease, the woman is or is not more than usually likely to develop septicaemia. The two cases related previously suffice to show that the chance of infection is probably much greater under these circumstances. The problem is limited by the nature of the available data to a more general enquiry with regard to their interrelationships, in which the following three methods of procedure suggest themselves:

(*a*) the relation between the seasonal prevalence of the diseases,
(*b*) the correlation between the incidence of the diseases in time, and
(*c*) the correlation between the incidence of the diseases in space.

And, in the consideration of the results, we must attempt to indicate whether the relationships, if any, are probably representative of associations between bacteriologically similar diseases, or an indirect relation from some other cause.

The three diseases, scarlet fever, erysipelas and diphtheria have been made the subject of enquiry into the relation between puerperal septicaemia and epidemic infectious diseases.

(*a*) *The Relation between the Seasonal Prevalence of Puerperal Septicaemia and that of Scarlet Fever, Erysipelas and Diphtheria.*

The deaths from puerperal septicaemia and these three infectious diseases in each month of the years 1921–1924 inclusive have been collected from the Annual Reports of the Registrar-General, and the seasonal distributions are compared in Table I and Diagram I, in which the deaths in each month are expressed as a percentage of the total deaths throughout the year. All of these diseases exhibit a remarkable uniformity in their prevalence with respect to

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season of the year. It may be objected with regard to this method of comparison in the case of deaths from puerperal sepsis that the number of births also varies with respect to season. On this point we cannot give the seasonal distribution with the same minuteness, since births are not given in the

Table I. *Showing the Seasonal Distribution of Deaths from Puerperal Fever, Scarlet Fever, Diphtheria and Erysipelas (England and Wales,* 1921–1924).

	Puerperal fever	Scarlet fever	Diphtheria	Erysipelas
January	9·7	12·3	13·1	11·1
February	8·4	9·7	11·2	9·8
March	10·2	10·0	9·8	10·2
April	9·7	8·8	8·4	10·3
May	9·2	8·6	7·4	8·3
June	7·1	6·9	6·3	7·9
July	7·2	5·6	5·4	6·0
August	6·4	5·4	6·2	5·9
September	7·2	5·6	6·4	5·0
October	7·6	7·8	7·6	6·9
November	8·0	8·5	8·3	8·6
December	9·3	10·8	9·9	10·0

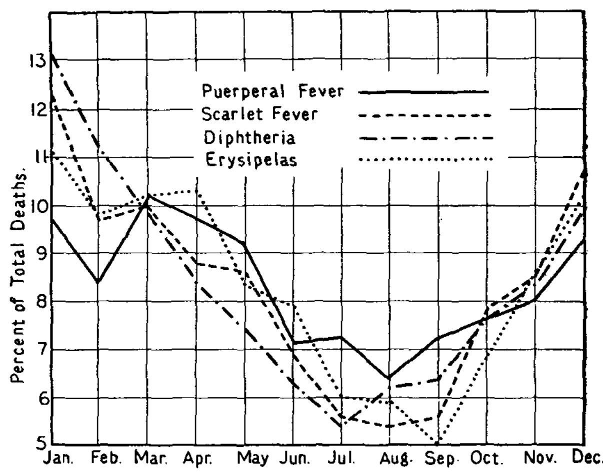

Diagram I. Showing the seasonal distribution of scarlet fever, diphtheria, erysipelas and puerperal fever in England and Wales (1921–1924).

reports by month of the year. The proportion of the total births which takes place in each of the four quarters of the year, however, is as follows (average of 1921–1924):

First quarter	... ...	25·5 per cent.
Second quarter	... ...	26·0 „
Third quarter	... ...	25·3 „
Fourth quarter	... ...	23·2 „

The seasonal fluctuation in the birth rate, as will be seen from the above figures, is not very pronounced. To correct the proportion of puerperal deaths at the several seasons for differences in the "exposed to risk" throughout

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the year, it is necessary to calculate the proportion of deaths which would occur if the births were uniformly distributed with respect to season. For example, in the last quarter of the year 24·9 per cent. of the total deaths take place, but only 23·2 per cent. of the total births. If 25 per cent. instead of 23·2 per cent. of the births had taken place, then the expected proportion of the total deaths in this quarter would be $24{\cdot}9 \times \frac{25{\cdot}0}{23{\cdot}2} = 26{\cdot}8$ per cent. A similar procedure carried out in the remaining quarters of the year gives the following distribution of deaths from puerperal fever corrected for seasonal changes in the birth rate:

First quarter	...	...	27·7 per cent.
Second quarter	...	...	25·0 „
Third quarter	...	...	20·5 „
Fourth quarter	...	...	26·8 „

However significant, therefore, we may regard the seasonal variation in the birth rate, it is of such a character that the seasonal distribution of the death *rate* from puerperal sepsis will become more apparent than would appear from the distribution of deaths alone.

It follows from this that the resemblance between the seasonal curves of these infectious diseases and of puerperal fever (see Diagram I) cannot be attributed in the latter disease to seasonal variations in the birth rate.

(*b*) *The Relation between the Secular Trends of Puerperal Sepsis and of Scarlet Fever, Diphtheria and Erysipelas.*

The temporal changes which have taken place in these diseases now fall to be considered. As previously indicated, Longstaff used this method in his investigation. Here I have considered the more recent and probably more reliable statistical information relating to these diseases in the period 1901–1925 inclusive. The rates of mortality are given in Table II and are graphically represented in the accompanying diagram (Diagram II). As will be seen from these figures, the death rate from each disease has fallen to some extent in this period. It follows, then, that if we correlate the actual rates of mortality we are certain to obtain a positive association. This obviously throws no light upon the problem to be considered, which is as follows: Each death rate is following some definite general trend (in these cases, downwards) within the period under review; but we note that in individual years deviations from that course occur. It is with these deviations that it is important to deal. We therefore wish to enquire whether or not the fluctuations in the death rate from puerperal septicaemia from the general trend which the disease is following are in any significant manner related to the deviations of these other diseases from their trends. When the puerperal sepsis death rate shoots up from the course it has previously been following, is there a concomitant rise in any or all of these other infectious diseases, and, if so, with which is the relation most stringent? The question is how to eliminate the disturbing influence arising from the similarity in the general course of all the diseases

Table II. *Showing the Rates of Mortality from Scarlet Fever, Diphtheria and Erysipelas per* 1,000,000 *Total Population and of Puerperal Fever per* 100,000 *Births in England and Wales in the years* 1901–1925 *inclusive.*

	Scarlet fever	Diphtheria	Erysipelas	Puerperal fever
1901	133	273	36	216
1902	148	237	39	203
1903	125	183	32	167
1904	112	170	36	165
1905	113	161	37	176
1906	101	178	35	164
1907	93	165	30	150
1908	80	158	24	140
1909	91	148	29	148
1910	66	120	23	136
1911	52	135	27	144
1912	55	118	25	140
1913	57	121	22	127
1914	77	158	30	156
1915	66	165	30	147
1916	39	153	21	138
1917	22	130	17	131
1918	29	140	17	128
1919	34	137	18	167
1920	38	151	22	181
1921	34	126	19	138
1922	36	107	18	138
1923	26	71	16	130
1924	23	64	17	139
1925	25	71	22	156

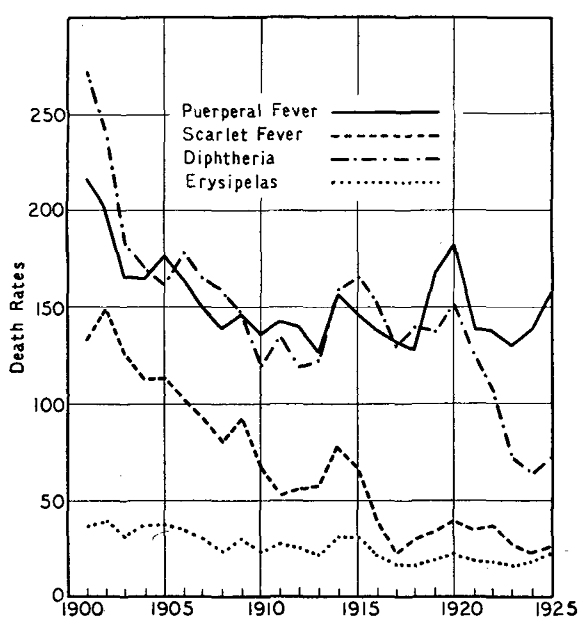

Diagram II. Showing the death rates from scarlet fever, diphtheria, erysipelas and puerperal fever in England and Wales (1901–1925).

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under consideration. An examination of the death rates (see Diagram II) shows that the downward course of each disease within the 25 years under review may be fairly well represented in a general way by a straight line. Consequently, to the individual death rates straight lines have been fitted by the method of successive approximation, and the differences, positive or negative, of the actual from the predicted death rates are the variables used for correlation purposes. Denoting puerperal sepsis by 1, scarlet fever by 2, diphtheria by 3 and erysipelas by 4, the coefficients of correlation found are as follows:

$$r_{12} = \cdot 6326 \pm \cdot 081 \qquad r_{23} = \cdot 3120 \pm \cdot 122$$
$$r_{13} = \cdot 6460 \pm \cdot 079 \qquad r_{24} = \cdot 6516 \pm \cdot 078$$
$$r_{14} = \cdot 4478 \pm \cdot 108 \qquad r_{34} = \cdot 1433 \pm \cdot 132$$

These relationships are well brought out in the accompanying diagram (Diagram III) showing the fluctuations above or below the general course of each of the diseases considered. All the coefficients involving puerperal septicaemia are significant in the statistical sense, and may be taken as indicative of a fairly strong tendency for deviations in this death rate to be associated with corresponding deviations in the death rates from scarlet fever, diphtheria and erysipelas. Excessive prevalence of each of these diseases co-exists on the average with excess prevalence of puerperal septicaemia, and *vice versâ*. With regard to the relative intensity of the associations, *i.e.* as to whether deviations in any one of these diseases are more closely related than the others to deviations in puerperal sepsis, little can be definitely said from these results. The correlation between diphtheria and puerperal septicaemia is arithmetically highest, followed closely by that with scarlet fever, and finally lowest of all that with erysipelas; but considered statistically these differences are evanescent. None of them is significant with regard to the probable error involved. The only possible conclusion at present is that each of these three diseases shows definite positive time relationships with the varying prevalence of puerperal fever, and that, so far as can be judged from these results, there is no apparent tendency for any one of them to have more intimate association than the others with puerperal fever. On the other hand, it may with equal confidence be affirmed that these relations are by no means perfect. Excessive prevalence of any one of these diseases is not always associated with excess prevalence of puerperal fever. Inspection of the diagram will reveal several exceptions to the general rule. The problem as to whether these significant relationships represent bacteriological affinities in these conditions or are simply expressions of the presence of some general factor or factors favouring the prevalence of all diseases of a contagious nature will be considered later.

From these statistics one further question may be answered. How close is the relation between variations in the prevalence of *all* of these three diseases and puerperal fever? In other words, how likely is it that when either scarlet fever, diphtheria or erysipelas or all of the diseases combined are above their normal prevalence, puerperal sepsis will also be above its general trend?

The answer to this may be made by appeal to a coefficient of multiple correlation. The coefficient deduced is $R_{1\cdot 234} = 0{\cdot}7626$. (The subscripts have the same meaning as before.) Therefore the conclusion must obviously be that when each or all of these infectious diseases rise or fall the chances are greatly in favour of a concomitant variation in the death rate from puerperal septicaemia.

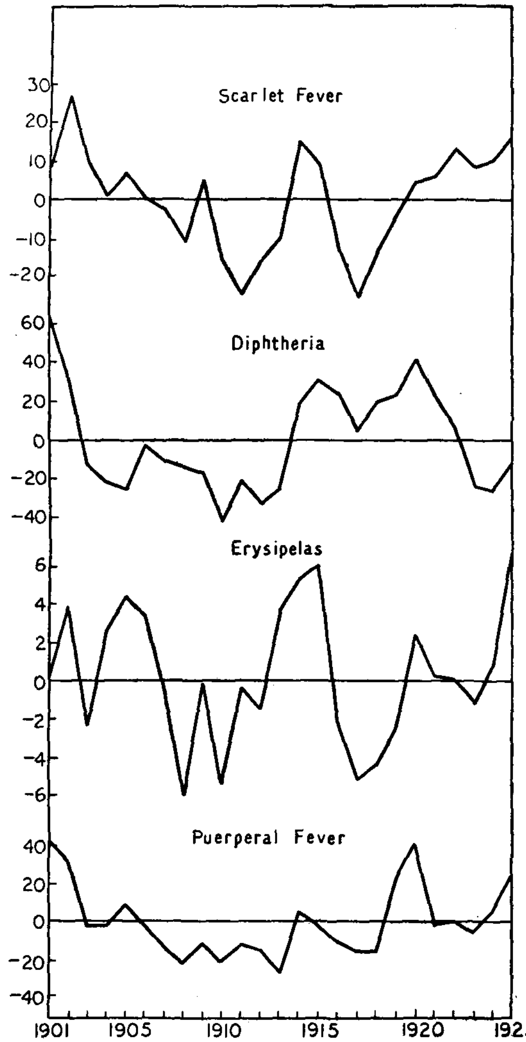

Diagram III. Showing the relation between the deviations from the trends of scarlet fever, diphtheria, erysipelas and puerperal fever (1901–1925).

In the procedure outlined in this section, the assumption has been made that the progressive secular changes in the rates of mortality have been effectively eliminated by considering only deviations from a straight line. That these changes are thus adequately eliminated gains support from the fact that if we represent the trends by equations involving the second and higher powers of the measure of time, the deviations of the rates of mortality from these curved regression lines are as closely correlated one with another as are the deviations of the variates from a straight line. The equations found for curve-fitting the death rates are these:

$$\begin{aligned} y_1 &= 153 - 1{\cdot}71\,\phi_1 + 0{\cdot}07\,\phi_2 - 0{\cdot}02\,\phi_3 \\ y_2 &= 67 - 4{\cdot}87\,\phi_1 + 0{\cdot}19\,\phi_2 - 0{\cdot}001\,\phi_3 \\ y_3 &= 146 - 5{\cdot}09\,\phi_1 + 0{\cdot}11\,\phi_2 - 0{\cdot}07\,\phi_3 \\ y_4 &= 25{\cdot}7 - 0{\cdot}86\,\phi_1 + 0{\cdot}027\,\phi_2 + 0{\cdot}002\,\phi_3 \end{aligned}$$

where y = the death rate in a given year x, x being measured from the mid-point of the series (1913), so that 1912 is represented by $x = -1$, 1911 by $x = -2$, etc., 1914 by $x = +1$ and so on,

$$\phi_1 = x, \quad \phi_2 = x^2 - \frac{n^2-1}{12}, \quad \phi_3 = x^3 - \frac{3n^2-7}{20}\,x,$$

and n is the number of observations. The subscripts of y have the meanings previously given.

Table III. *Showing the Changes in the Coefficients of Correlation between Deviations from the Trends of Puerperal Fever, Scarlet Fever, Diphtheria and Erysipelas when Secular Changes are eliminated by Different Equations.*

	Straight line	Parabola	Cubic
Puerperal fever–erysipelas	·4476 ± ·108	·3986 ± ·113	·5114 ± ·100
Puerperal fever–scarlet fever	·6326 ± ·081	·3108 ± ·122	·3236 ± ·121
Puerperal fever–diphtheria	·6460 ± ·079	·5892 ± ·087	·4917 ± ·102

Table III is given to show how small and irregular are the differences in the coefficients of correlation which are found when the variables used are the deviations from (1) a straight line, (2) a parabola and (3) a cubic.

These results would appear to justify the conclusion that there has been a definite tendency within the present century for the mortality from puerperal sepsis to fluctuate from its general course in conjunction with similar variations in the death rates from these infectious diseases.

(c) *The Relation between the Geographical Distribution of Puerperal Sepsis, Scarlet Fever, Diphtheria and Erysipelas.*

In the previous section I have shown that, on the average, deviations from the trends of the measures of several diseases are correlated, and that this association is not more stringent between puerperal septicaemia and scarlet fever or erysipelas than between the first-named and diphtheria. The correlations in space remain for investigation, *i.e.* we now consider simultaneous variations of the measures of the four diseases at different places. In this task although we are freed from one of the difficulties of the time comparison, in that our allowance for the effect of secular trend is empirical, we introduce a new difficulty, *viz.* the very wide range of local variations of factors which may or may not influence the various correlations. This part of the investigation should, in my opinion, be studied in the light of the following considerations. Having regard to modern bacteriological teaching, we cannot doubt that puerperal fever, erysipelas and scarlet fever have a closer pathological affinity one with another, by virtue of their known associations with streptococcal infection, than has puerperal septicaemia with diphtheria since, in at least a larger proportion of cases, streptococcal infection is not such an important feature of diphtheria. If therefore we find by the method of correlation that puerperal fever is as closely associated, whether negatively or positively is irrelevant, with diphtheria as with either of the other diseases, we are entitled to conclude that the association does not strengthen the view that a common bacteriological factor is responsible. We may, in fact, regard the puerperal fever-diphtheria correlation as a statistical control.

Table IV.

A. *Showing the Correlations between Puerperal Fever Notification Rates and the Notification Rates of Scarlet Fever, Erysipelas and Diphtheria.*

	London	County Boroughs	Administrative Counties
(*a*) 1911–1913			
Scarlet fever	$-\cdot 087 \pm \cdot 126$	$-\cdot 062 \pm \cdot 078$	$-\cdot 015 \pm \cdot 103$
Erysipelas	$-\cdot 034 \pm \cdot 127$	$\cdot 089 \pm \cdot 077$	$-\cdot 021 \pm \cdot 103$
Diphtheria	$-\cdot 092 \pm \cdot 126$	$-\cdot 152 \pm \cdot 076$	$-\cdot 105 \pm \cdot 102$
(*b*) 1921–1923			
Scarlet fever	$\cdot 093 \pm \cdot 126$	$\cdot 034 \pm \cdot 074$	$\cdot 398 \pm \cdot 087$
Erysipelas	$\cdot 240 \pm \cdot 120$	$\cdot 254 \pm \cdot 071$	$\cdot 248 \pm \cdot 096$
Diphtheria	$-\cdot 127 \pm \cdot 125$	$\cdot 214 \pm \cdot 071$	$\cdot 405 \pm \cdot 086$

B. *Showing the Correlations between Puerperal Fever Death Rates and the Notification Rates of Scarlet Fever, Erysipelas and Diphtheria.*

	London	County Boroughs	Administrative Counties
(*a*) 1911–1913			
Scarlet fever	$-\cdot 072 \pm \cdot 126$	$\cdot 012 \pm \cdot 077$	$\cdot 136 \pm \cdot 101$
Erysipelas	$\cdot 006 \pm \cdot 127$	$\cdot 169 \pm \cdot 076$	$\cdot 078 \pm \cdot 102$
Diphtheria	$-\cdot 092 \pm \cdot 126$	$-\cdot 156 \pm \cdot 076$	$\cdot 201 \pm \cdot 099$
(*b*) 1921–1923			
Scarlet fever	$-\cdot 271 \pm \cdot 118$	$-\cdot 053 \pm \cdot 074$	$\cdot 474 \pm \cdot 080$
Erysipelas	$-\cdot 310 \pm \cdot 115$	$\cdot 112 \pm \cdot 074$	$\cdot 359 \pm \cdot 090$
Diphtheria	$-\cdot 477 \pm \cdot 099$	$\cdot 007 \pm \cdot 074$	$\cdot 346 \pm \cdot 091$

Table IV (*a*) and (*b*) shows the correlations based on the triennia1911–1913 and 1921–1923 between the notification rates and the mortality rates of puerperal fever and the notification rates of scarlet fever, diphtheria and erysipelas for the 28 Metropolitan Boroughs, 82 County Boroughs (75 for 1911–1913) and 43 Administrative Counties. Here we see a wide diversity of arithmetical values but complete uniformity in respect of the test above proposed. In the period 1911–1913, using notification rates of puerperal fever, *all* the correlations are insignificant. In 1921–1923 those for Administrative Counties are statistically significant, but the correlation involving diphtheria is of the same order of magnitude as the other two. When death rates are used, we have uniform non-significance of the coefficients in 1911–1913, and in 1921–1923 a contrast in sign between the London results and those for Administrative Counties. This contrast is as striking when the diphtheria rate is the other variable as when we use erysipelas or scarlet fever. In other words, whatever may be the factors which produce these associations they are no more stringent for one pair than for another. The variations of magnitude between 1911–1913 and 1921–1923 also imply that we are not dealing with a constantly acting group of factors. The objection to the use made in the above argument of the diphtheria rate as a control, *viz.* that diphtheria may be in fact so intimately correlated with the other diseases both in time and place that it is an inadequate control is confuted by the following results. From Table V it appears that

Table V. *Showing the Correlations between the Notification Rates of Diphtheria, Scarlet Fever and Erysipelas.*

	London	County Boroughs	Administrative Counties
(*a*) 1911–1913			
Diphtheria and scarlet fever	·537 ± ·091	·068 ± ·078	·144 ± ·101
Diphtheria and erysipelas	·103 ± ·126	·088 ± ·078	·088 ± ·102
(*b*) 1921–1923			
Diphtheria and scarlet fever	·746 ± ·057	·282 ± ·069	·424 ± ·084
Diphtheria and erysipelas	·388 ± ·108	·101 ± ·074	·114 ± ·102

although for one period and in one set of geographical subdivisions the correlation between the incidence rates of scarlet fever and diphtheria is substantial, it is not uniformly high even for scarlet fever and diphtheria; but between the incidence rates of diphtheria and erysipelas there is not any substantial correlation. Passing now to the time sequence, we find that the correlation between deviations from the linear trends of scarlet fever and diphtheria rates is $0{\cdot}312 \pm 0{\cdot}122$, and between the deviations of diphtheria and of erysipelas rates $0{\cdot}143 \pm 0{\cdot}132$. Neither value is statistically significant. We are entitled to conclude therefore that diphtheria rates may fairly stand as a statistical control.

Conclusion.

The result of the present investigation is to suggest that such correlation in time and place between the prevalence or mortality of puerperal fever and the prevalence of erysipelas and scarlet fever as can be demonstrated cannot be taken to support the opinion that there is an etiological factor common to the three diseases.

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