STUDIES IN THE MEANING AND RELATIONSHIPS OF BIRTH AND DEATH RATES.

IV.

On the Range of Instances in which Geometrical Progressions describe numerically processes of life, i.e. those processes which might be explained by a monomolecular reaction.

By JOHN BROWNLEE, M.D., D.Sc.

In recent years it has been found that *in vitro* many ferments, etc., lose their power of action at a rate corresponding to the monomolecular reaction, *i.e.* if the amount of the substance present at the beginning is denoted by unity, and, if after a certain period of time only one half of the substance remains active, then it may be predicted that at the end of an equal period of time, one half of one half, or only one quarter of the original amount, will still retain its power of action. It is not necessary to give examples, they are sufficiently well known.

In actual living organism, however, this relationship can be just as well demonstrated in a large number of instances, some immediately obvious, others requiring some care to establish. The oldest known example, discovered by Gompertz, is the increase of the death rate with age. Thus the average death rate among males (1858–1901) as given by the Registrar-General is for the age period 55–65, 33·3 per mille, for 65–75, 68·3 per mille, 75–85, 147·4 per mille, and for the ages above 85 as 308·6 per mille.

It will be noticed that the death rate approximately doubles itself with each ten years' increase of age. For high ages in fact this relation is an excellent interpolation formula.

It is not necessary to give in this place cumulative evidence as all that is required for the present purpose is to show that the phenomenon is of some generality. As typical examples it is to be noted

https://doi.org/10.1017/S0022172400006100 Published online by Cambridge University Press

that the following sequence of values are described by a geometrical progression:

(1) The rate of decrease in the case mortality of infectious diseases among children as age increases.

(2) The rate of increase in the case mortality of infectious diseases among adults as age increases.

(3) The rate of decay of the protective power of vaccination as age increases.

(4) The decay of the natural immunity of children and the growth of natural immunity of adults towards certain diseases as age increases.

(5) The loss of infectivity of an organism during an epidemic.

Some of the data referring to these instances ("The Relation of the Monomolecular Reaction to Life Processes and to Immunity," *Proc. Roy. Soc. Edin.* 1911) have already been published, but the figures referring to scarlet fever are reproduced.

The case mortality from scarlet fever is highest in children between one and two years, and thereafter declines from year to year. The rate of decline is such that the case mortality during each year of life is three-quarters that of the preceding, as can be easily seen from the table (Table I) in which the case mortalities taken from the statistics of Glasgow and Manchester are given in parallel columns with the appropriate theoretical values, these being the only two cities for which statistics can be given for the several years up to ten. Though the type of scarlet fever prevalent among children in Glasgow is considerably more severe than that in Manchester, it is worthy of special notice that the ratio of decrease is identical. The case mortality for measles varies in the same way, but in this instance the ratio of diminution between the case mortalities of succeeding years of life is not ·75 but ·65; that is, children tend to grow out of the fatal period more quickly. Thus after three years the susceptibility to death in the case of scarlet fever has only fallen to ·42 of that of the epoch of commencement, while in the case of measles it has fallen to ·28.

To these examples the figures relating to diphtheria are added, as they have not been shown to obey the same law. The case mortalities are those obtaining in the city of Manchester for the ten years 1893–1903. In Table I these figures and the progression fitted by the geometrical law are given in parallel columns. The ratio found in this case between the mortality of successive years of age is conspicuously higher, namely, ·86, a figure much higher than in the cases of measles and scarlet fever.

https://doi.org/10.1017/S0022172400006100 Published online by Cambridge University Press

TABLE I.

Showing the case mortalities of scarlet fever and diphtheria fitted to curves of the form $y = ae^{-\kappa x}$.

	Scarlet Fever				Diphtheria	
	Glasgow		Manchester		Manchester	
Age period	Actual	Theoretical	Actual	Theoretical	Actual	Theoretical
1– 2	24·3	22·2	19·3	19·3	58·4	58·1
2– 3	16·5	16·5	14·7	14·2	51·2	50·1
3– 4	12·6	12·4	12·2	10·6	40·9	43·1
4– 5	9·1	9·3	8·7	7·8	36·1	36·9
5– 6	7·0	7·0	5·7	5·8	33·2	31·8
6– 7	4·1	5·2	4·5	4·3	27·9	27·3
7– 8	3·6	3·9	3·4	3·2	24·6	23·6
8– 9	3·1	2·9	2·2	2·3	20·2	20·2
9–10	2·2	2·2	—	—	11·6	17·3
10–15	—	—	—	—	7·2	10·8
15–20	—	—	—	—	4·4	4·4

II. In this group of instances the death rate steadily increases with age. The figures for smallpox and typhus have already been published and the only point of importance is the ratio of increase of the case mortality with age. With smallpox in Gloucester, the case mortality increases with each ten years of age in the ratio 1·30. With regard to typhus the ratio is the same for Glasgow and London and is considerably larger than that just given, namely 1·46.

In more extreme age diarrhoea furnishes a good example.

For the age periods 45–55, 55–65, 65–75, 75– , the death rates per million living during the decade 1891–1900 were respectively 95, 243, 715, 2151 for males, and 76, 226, 703, 2011 for females, showing a rough ratio between successive numbers of nearly 3, the greatest ratio hitherto found. Diarrhoea is an infectious disease which is ubiquitous, and it may be taken that all are alike exposed to infection. This curve thus represents the combined effects of susceptibility to disease and case mortality.

Of a like nature is the phenomenon shown by the influenza statistics. As this disease caused no mortality at all in London in the late eighties, the figures relating to the deaths may be taken as practically true when the years of the great epidemics 1890, 1891 and 1892 are considered. It may be considered that all ages alike succumbed to infection and that the death rates at different ages are thus equivalent to case mortalities. When the ratio of increase is examined, however, it is found to be practically identical in its value with that occurring between the death rates from all causes, given earlier in the paper. With each

https://doi.org/10.1017/S0022172400006100 Published online by Cambridge University Press

ten years of age from 45 upwards, the death rate, both for males and females, practically doubles itself. Influenza may thus be looked upon more as a factor accelerating death than as a disease with a special mortality of its own. The figures are given in the adjoining table.

TABLE III.

Death rates per thousand at different ages from influenza for London during the years 1890, 1891 *and* 1892.

Age period	Death rate per thousand Male	Female
45–55	·79	·59
55–65	1·33	1·28
65–75	2·64	2·59
75–	5·61	5·07

III and IV. The figures regarding the decay of the protective power of vaccination treated by the method of correlation have already been published[1], and in this place the ratio of decay is measured in a different manner. An analysis of the susceptibility to certain diseases at each age is made. It involves a double problem; firstly, in youth, either owing to special insusceptibility to disease, *e.g.* enteric fever, or to acquired insusceptibility, *e.g.* smallpox after vaccination, there is a period in which the cases of the disease are few; secondly, as age advances a special immunity developes. It is apparently a fact, and a fact somewhat curious, that these two forms of immunity are additive, or that the protection at any moment is proportional to their sum. Three examples are considered. In the first place the age distribution of susceptibility to smallpox among the vaccinated is examined. The most important data for this are contained in Dr Barrie's report on the epidemic of smallpox in Sheffield in the year 1887. Here owing to the fact that a census was taken as to the numbers of vaccinated in the whole population, the susceptibility to smallpox of persons at different ages can be calculated. This is exceedingly important because owing to the manner in which towns recruit their populations from different districts, very marked variations in the number of vaccinated and unvaccinated at different ages may occur. The drawback to Dr Barrie's Census is that he has not separated between those who are definitely and those who are doubtfully vaccinated as is usually done. There are thus far too many children under five years of age as compared with the statistics of other places. Some correction has therefore to be made to obtain the probable number of those who

[1] *Loc. cit.*

https://doi.org/10.1017/S0022172400006100 Published online by Cambridge University Press

were definitely vaccinated. This is done on the basis of the Glasgow epidemic by assuming that from 0 to 5 years 45 per cent. of the total cases occurred among definitely vaccinated children and from 5 to 10 years 90 per cent. At the other ages correction is immaterial as insusceptibility to smallpox depends much more upon the natural immunity due to age than on the protection due to vaccination.

Two factors determine the distribution of susceptibility, one, the protection due to vaccination great in youth and gradually disappearing, the rate of its disappearance being described by the terms of a geometrical progression: the other factor, the increase of natural immunity with age also described in a like manner. The fitting of this compound curve to the statistics is largely a matter of trial and error. In the accompanying table (Table V) are shown in parallel columns the total number of cases; the susceptibility at each age period; then the reciprocal of the latter: in the next two columns this analysed into its two parts: these two latter columns summed: the number of cases to which they correspond calculated and compared with the number given by observation. The difference is remarkably slight; when the usual calculations are made it is found that $\chi^2 = 3{\cdot}24$, which gives the probability of the analysis $P = {\cdot}95$.

The epidemic of miliary fever in Oise in 1827 is next analysed. For this a table constructed in the manner described above is also given. It is found that $\chi^2 = 6{\cdot}0$, which gives a probability $P = {\cdot}53$. Though not so high as that shown for smallpox, it must be accounted a good fit.

The cases of enteric fever in London are given as the last example and though they do not give a good fit ($\chi^2 = 18{\cdot}16$, due to the very large number of cases analysed, over five thousand) yet the curve is essentially similar and the divergence much less than that found by Prof. Pearson in his analytical graduation of the curve. We thus have the susceptibility to certain diseases described by a curve of different form to any hitherto proposed. The graduation which has been discussed is obviously described by the formula

$$y = \frac{a}{e^{-mx} + e^{nx}}.$$

It is thus possible to describe these three diseases in a manner capable of being explained by the monomolecular reaction. The manner in which the ratios of decay and growth of immunity vary is exceedingly interesting and the collected results are given in the accompanying table.

https://doi.org/10.1017/S0022172400006100 Published online by Cambridge University Press

TABLE IV.

	Rate of decay of the immunity of youth per 5 years	Rate of growth of old age immunity per 10 years
Smallpox	·192	1·91
Miliary fever	·523	1·35
Enteric fever	·182	2·15

It is to be noticed that each disease has its special method of variation.

It may be remarked that though these adult diseases have been thus easily analysed others have more complex immunity phenomena resembling in this respect the diseases of childhood.

These will be considered later after the method of treating a sum of monomolecular reactions has been described.

V. It is not necessary to discuss the curve of an epidemic in this place but only to notice that it can be approximately accounted for if the organism loses its infectivity at a rate something approaching a geometrical progression.

Appendix.

On the curve $y = \dfrac{a}{be^{-mx} + ce^{nx}}$.

With change of origin this equation can be put in the form

$$y = \frac{ae^{px}}{e^{-mx} + e^{mx}}.$$

The curve thus contains three constants and is of some interest. It allows finite susceptibility at any age and describes the course of immunity during life in a definite formula. It is therefore superior to graduation curves which seek to smooth merely the numbers of cases and tell nothing of what is going on. To calculate the area and moments the term in the numerator is expanded and each term severally integrated from positive to negative infinity. Thus

$$\int_{-\infty}^{\infty} \frac{e^{px}dx}{e^{-mx} + e^{mx}} = \int_{-\infty}^{\infty} \frac{dx}{e^{mx} + e^{-mx}} + p\int_{-\infty}^{\infty} \frac{xdx}{e^{mx} + e^{-mx}} + \frac{p^2}{1 \, . \, 2}\int_{-\infty}^{\infty} \frac{x^2dx}{e^{mx} + e^{-mx}} + \ldots$$

$$= 2\left\{\frac{\pi}{2m} + \frac{p^2}{1 \, . \, 2}\left(\frac{\pi}{2m}\right)\right\}^3 E_1 + \frac{p^4}{1 \, . \, 2 \, . \, 3 \, . \, 4}\left(\frac{\pi}{2m}\right)^5 E_2 + \ldots$$

where E_1, E_2, etc., are Euler's numbers,

$$= \frac{\pi}{m}\sec\frac{p\pi}{2m}.$$

https://doi.org/10.1017/S0022172400006100 Published online by Cambridge University Press

TABLE V.

Showing the fitting of curves of susceptibility to the form $y = \dfrac{a}{be^{-mx} + ce^{nx}}$.

(a) *Smallpox, Sheffield,* 1887–8:

Age period	No. of cases	Susceptibility per 1000	Reciprocal	Analysis		Sum	Theoretical no. of cases
0– 5	43[1]	253	88·844	·752	91·221	91·973	41·1
5–10	215·5[1]	603	18·518	1·038	17·546	18·584	214·8
10–15	782	2067	4·837	1·433	3·375	4·808	787·0
15–20	1240	3987	2·508	1·978	·649	2·627	1184·0
20–25	950	3480	2·873	2·731	·125	2·856	956·0
25–35	1019	2194	4·558	4·438	·024	4·462	1041·0
35–45	429	1182	8·460	8·460	·005	8·465	428·0
45–55	156	620	16·129	16·129		16·129	156·0
55–65	66	3033	33·045	30·740		30·740	68·4

[1] Corrected as described in the text.

$\chi^2 = 3{\cdot}24$. $P = {\cdot}91$.

(b) *Miliary fever, Oise,* 1827:

Age period	No. of cases	Susceptibility per 1000	Reciprocal	Analysis		Sum	Theoretical no. of cases
0–10	77	11·3	88·496	2·385	80·000	82·385	82·7
10–20	205	39·3	25·445	3·233	21·909	25·142	207·9
20–30	429	101·9	9·814	4·381	6·000	10·381	405·5
30–40	501	128·3	7·811	5·938	1·642	7·580	516·9
40–50	410	119·9	8·340	8·047	·449	8·496	402·5
50–60	208	98·8	10·111	10·905	·123	11·028	190·7
60–70	101	73·7	13·569	14·778	·033	14·811	92·5
70–80	15	33·0	27·076	20·027	·010	20·037	20·2

$\chi^2 = 6{\cdot}21$. $P = {\cdot}51$.

(c) *Enteric fever, London,* 1871–93:

Age period	No. of cases	Susceptibility per 1000	Reciprocal	Analysis		Sum	Theoretical no. of cases	Prof. Pearson's distribution
0– 5	266	530·3	18·858	·636	18·150	18·786	267	353
5–10	1143	2516·7	3·974	·932	3·300	4·232	1072	1236
10–15	2019	4848·4	2·063	1·386	·600	1·986	2097	1833
15–20	1955	4690·3	2·131	2·031	·090	2·121	1964	1735
20–25	1319	3078·5	3·248	2·975	·019	2·994	1426	1374
25–35	1360	1895·4	5·275	5·275	·003	5·278	1360	1433
35–45	462	889·1	11·248	11·367	·000	11·367	457	470
45–55	138	374·4	27·710	24·495	·000	24·495	156	136
55–65	22	121·9	82·056	51·400	·000	51·400	42	20[1]

Present fitting: $\chi^2 = 22{\cdot}3$, $P = {\cdot}005$; Prof. Pearson's fitting: $\chi^2 = 83{\cdot}1$, $P = 0$.

[1] For 55 to 60 as against 14.

https://doi.org/10.1017/S0022172400006100 Published online by Cambridge University Press

The moments about the origin are obviously obtained by differentiating this with regard to p. Transferred to the centroid vertical, which is at a distance

$$\frac{\pi}{2m}\sec\frac{p\pi}{2m}\tan\frac{p\pi}{2m}$$

from the origin, the values are

$$\mu_2 = \left(\frac{\pi}{2m}\right)^2 \sec^2\frac{p\pi}{2m},$$

$$\mu_3 = 2\left(\frac{\pi}{2m}\right)^3 \sec\frac{p\pi}{2m}\tan\frac{p\pi}{2m},$$

$$\mu_4 = \left(\frac{\pi}{2m}\right)^4 \left(4\sec^2\frac{p\pi}{2m}\tan\frac{p\pi}{2m} + 5\sec^4\frac{p\pi}{2m}\right).$$

Whence

$$\beta_1 = 4\sin^2\frac{p\pi}{2m},$$

$$\beta_2 = 4\sin^2\frac{p\pi}{2m} + 5,$$

$$F = 2\beta_2 - 3\beta_1 - 6$$

$$= 4 - 4\sin^2\frac{p\pi}{2m}.$$

The curve would thus be very easily fitted by the moments were it possible to obtain these from the statistics. It has the moment relationship of Type IV or Type VI according as $p <$ or $> \frac{m}{3}$ approximately. The curve in general will be asymmetrical because the ratio of the decay of the natural immunity of childhood is not identical with that at which immunity increases with age.

https://doi.org/10.1017/S0022172400006100 Published online by Cambridge University Press