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The Relation of the Mono-Molecular Reaction to Life-Processes and to Immunity.

By John Brownlee, M.D., D.Sc.

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XLIII.—The Relation of the Mono-Molecular Reaction to Life-Processes and to Immunity. By John Brownlee, M.D., D.Sc.

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Some of the relationships, such as those between toxins and antitoxins, discovered during the last twenty years have lately been investigated by Arrhenius. It has been found by this observer that many of these

Agglutinating Power of the Blood.

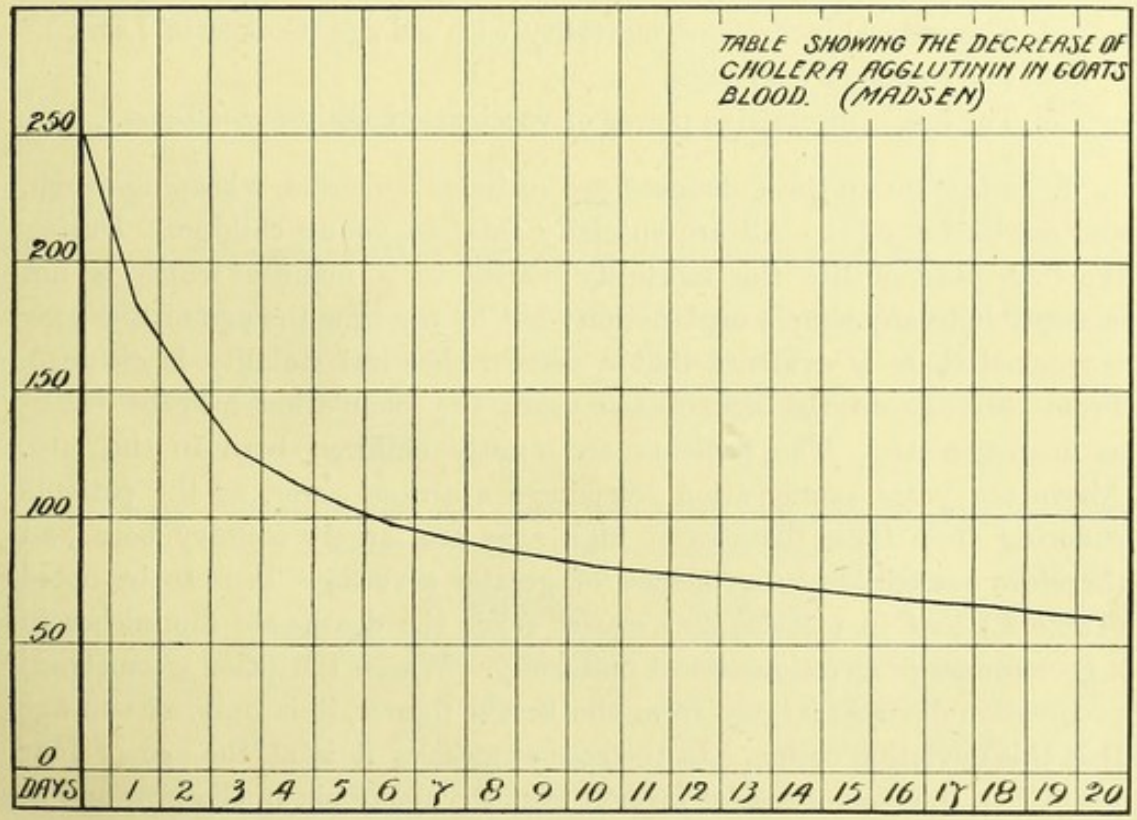

Diagram I.

processes can be adequately represented by the equations which govern homogeneous mass reactions; for instance, the rates of the disappearance of diphtheria antitoxin and of typhoid agglutinin from the circulation are described at least empirically by such a formula (Diagram I.) (1). Some years ago, in a communication to this Society on the laws of epidemics (2), I showed that the course of an epidemic could be accounted for if the organism, having a high infectivity at the beginning of the epidemic, lost

its power of infecting thereafter at a rate corresponding to a geometrical progression. Miss Chick (3), in some experiments on disinfection, came to a like conclusion, finding that, in the application of a germicide to spore-bearing organisms, the number of survivors at the end of each period of time obeyed the same law. Miss Chick's problem is, however, fundamentally different from mine: their relationships will be discussed later. Such observations suggested a search through the records of disease for analogous examples. Five such in all have been discovered up to the present—

1. The decline of the death-rate in children's zymotic diseases from birth to the age of ten years.
2. The increase of mortality in zymotic diseases of adults with increase of age.
3. The general increase of mortality with old age (Gompertz' Law).
4. The course of epidemics.
5. The loss of protective power of vaccination against small-pox.

1. In this group three diseases are included—measles, whooping-cough, and scarlet fever (4). All are specially fatal to young children. During the first year of life the mortality varies in a manner which is not susceptible to any simple explanation; but by the time the age of one year is reached there is evidence that a certain chemical stability is attained. From this age to the age of ten years the population may be taken as homogeneous. The patients are mostly children born in the city. Above ten years immigration introduces a serious error, as the patients suffering from these diseases at high ages are largely country born, and therefore susceptible to an attack of greater severity. It is to be noted (Table I.) that in measles and scarlet fever the death-rate diminishes in a geometrical progression almost uniformly. Where the fitted geometrical progression deviates largely from the actual figures, it is only at one age that this deviation occurs. In the case of measles it is at the age of four years. In the case of scarlet fever it is at the age of six in Glasgow and at that of three in Manchester. When the fitting of these curves is tested by Pearson's method of estimating goodness of fit the value of P is fairly large, but in each case at least two-thirds of the value of χ^2 is due to one year, and in each case a different year. We may, then, hold it probable that the deviation is accidental. The case of whooping-cough is somewhat different, but the selection for admission in this case is much more stringent; specially ill children only are chosen, or those whose home circumstances are very bad, so that at the higher ages there will be a larger proportion of severe cases. Thus *a priori* a concordance of fact with theory should

TABLE I.

Table showing the Case Mortality at Ages from 1 Year to 10 Years in the City of Glasgow Fever Hospital, Belvidere, for Measles, Whooping-cough, and Scarlet Fever, with a like Table added for Comparison for Scarlet Fever in Manchester.

Age Period.	Measles.		Whooping-cough.		Scarlet Fever.				Aberdeen	
					Glasgow.		Manchester.			
	Actual C. M. %.	Theor. C. M. %.	Actual C. M. %.	Theor. C. M. %.	Actual C. M. %.	Theor. C. M. %.	Actual C. M. %.	Theor. C. M. %.	Actual	Theor.
−1									12·7 10·9 11·8	10·2
1–2	26·1	25·0	38·0	38·0	24·3	22	19·3	19·3	12·3 7·5 10·2	7·7
2–3	15·5	16·0	25·6	25·1	16·5	16·5	14·7	14·2	8·5 7·4 8·0	5·8
3–4	10·4	10·2	15·3	16·1	12·6	12·4	12·2	10·6*	5·9 5·1 5·5	4·3
4–5	5·0	6·5*	11·7	11·7	9·1	9·3	8·7	7·8	4·1 5·4 4·8	3·2
5–6	4·3	4·2	9·1	7·2*	7·0	7·0	5·7	5·8	2·3 3·4 2·9	2·4
6–7	2·7	2·7	6·6	4·7*	4·1	5·2*	4·5	4·3	1·7 1·9 1·8	1·8
7–8	1·4	1·7	…	…	3·6	3·9	3·4	3·2	1·5 1·2 1·3	1·4
8–9	1·9 { 1·5	1·1 } 1·8	…	…	3·1	2·9	2·2	2·3	1·5 1·7 1·6	1·6
9–10	{ ·4	·7 }	…	…	2·2	2·2			1·7 0·95 1·3	0·4

$\chi^2 = 8{\cdot}3$ $P = {\cdot}40$ $\chi^2 = {\cdot}83$ $P > {\cdot}80$ $\chi^2 = 7{\cdot}9$ $P = {\cdot}43$ $\chi^2 = 7{\cdot}2$ $P = {\cdot}53$

* Ages at which divergence of fact from theory is greatest.

not be expected. As a matter of fact, from one year to five years the concordance is excellent, but thereafter it falls away.

A certain check on the value of this comparison is seen in Table II.,

TABLE II.

Table showing the Factor which represents the Rate of Loss of Mortality in each of the above Cases.

	Scarlet Fever.		Measles.	Whooping-cough.
	Glasgow.	Manchester.	Glasgow.	Glasgow.
Factor . . .	·75	·74	·64	·65

where the factor which expresses the ratio of the decline from year to year is given. With regard to scarlet fever, it is to be noted that, though the disease is at each age more severe in Glasgow than in Manchester, yet the progressions from year to year have the same ratio. This is in strict accordance with what I have elsewhere stated, that the average illness only is due to the virulence of the germ, and that the relative illness depends wholly on the susceptibility of the persons affected. When measles and whooping-cough are compared, though the values of the ratios differ considerably from that of scarlet fever, they have a marked concordance,

a fact to be expected, as the chief cause of death is in both instances the same, namely, broncho-pneumonia.

2. In this group the evidence is very scanty and not of the highest value. The essential condition, namely, the homogeneous population, can hardly be attained. For instance, in Glasgow, small-pox draws such a large number of its victims from the model lodging-house population, a population of inferior resistance and of lower mean ages, that the figures for the class mortality at middle ages cannot be compared with those at high ages. For this disease the epidemic in Gloucester (5) in 1895–6 has been chosen as affording more homogeneous material. With regard to typhus, on the other hand, Glasgow, with its large Irish population, among whom the disease chiefly spreads, affords more homogeneous material than London. When, however, data are selected in this manner their importance is much diminished. It is further to be noted that an epidemic attacking a practically virgin population may be expected to give better evidence than one where the susceptible persons have largely been protected by an attack of the disease before they arrived at old age.

TABLE III.

Table showing the Increase of Case Mortality in Typhus Fever at Ages above 25 Years in Glasgow and London.

Age Period.	Glasgow, 1865–1871.				London.			
	Cases.	Deaths.	Case Mortality.		Cases.	Deaths.	Case Mortality.	
			Actual.	Theor.			Actual.	Theor.
25–35	841	147	17·6	17·7	3245	574	17·6	17·7
35–45	648	183	28·3	26·0	2965	842	28·3	26·3
45–55	309	127	41·0	38·2	1829	834	45·4	38·2*
55–65	107	57	53·0	54·9	881	479	54·4	54·9
65–75	20	16	80·0	82·4	272	203	74·7	82·4

* Age when the law does not hold.

$\chi^2 = 2$ P = ·74 $\chi^2 = 25·5$ P = ·0001

In Table III. a comparison of the death-rate of typhus fever in Glasgow (4) and London (6) for the times when that disease was common is given. It is to be noted in the first place that at these age periods—25–35, 35–45, and 55–65—the case mortalities in both cities are practically identical. These were therefore taken as a basis, and a geometrical progression fitted by the method of least squares. The result for Glasgow is very good, but from London far from satisfactory. The error is again almost wholly at one age period, 45–55.

TABLE IV.

Table showing the Case Mortality for Small-pox among the Vaccinated, Gloucester, 1895–6.

Age Period.	Cases.	Deaths.	Case Mortality.	
			Actual.	Theor.
20–30	367	23	6·2	8·1*
30–40	272	29	10·6	10·6
40–50	142	21	14·8	13·8
50–60	63	12	19·8	18·0
60–70	34	8	23·5	23·6
70–80	13	4	30·8	30·8

* Age when the law does not hold.

For all ages $\chi^2 = 2{\cdot}4$ P = ·62.
For ages above 30 $\chi^2 = {\cdot}3$ P = ·91.

With regard to small-pox, Table IV., the Gloucester figures show a very good agreement between fact and theory. From 30 upwards the concordance is exact. The theoretical figures were fitted to the mortality rates for the latter years, and that for the age period 20–30 thence calculated. When the whole series thus obtained is considered, the value of P is not specially high, but for the period above 30 years the fit is exceptionally good.

3. *Gompertz' Law.*—This law is the product of an earlier science, and has almost been forgotten. Briefly expressed, it is to the effect that the liability to death increases in a geometrical progression with age. Its truth is undoubted for all ages above 50 for both sexes. In this law Makeham made a change which rendered it much more convenient to actuaries, but which obscured the biological significance of the original statement. The following figures from the Registrar-General's tables for England sufficiently explain the facts:—

TABLE V.

Showing the Average Death-rate in Males and Females at Ages 55 and Upwards for the Period 1858–1901.

Age Period.	Males.	Females.
55–65	33·3	28·1
65–75	68·3	60·0
75–85	147·4	133·3
85–	308·6	281·9

The death-rate thus approximately doubles itself every ten years.

4. *The Law of the Epidemic.*—It is not necessary to discuss this again fully. In my two communications to this Society (2), I have shown that the decline of infectivity of an organism must follow very closely a geometrical progression.

5. *The Loss of Protective Power of Vaccination against Small-pox.*—This is the only example in which the data are in the least sufficient to permit of the calculation of the rate of loss of acquired immunity. The subject, however, is specially difficult. It is not sufficient to take the case rate for each age period of population and examine that, as has been done in previous instances. For, in the first place, both vaccinated and unvaccinated are specially susceptible to small-pox at the ages of 10–15, and, in the second place, old age confers a very real immunity against small-pox. In one instance alone do data exist which permit the elimination of these factors, namely, the epidemic in Sheffield in 1887–88 (7), discussed in a former paper. In this case a census of the vaccinated and unvaccinated was made, so that for each age period we have the numbers of both vaccinated and unvaccinated, and the numbers of cases of small-pox occurring among each.

This permits the calculation of the coefficients of correlation showing the degree of protection present (8). The values of these coefficients and of the geometrical progression fitted to them are given in the accompanying diagram (Diagram II.). As will be seen, the correspondence is very fairly close. Certain of the values are obviously too low, and certain others too high. When these are adjacent it will be noted that the curve almost exactly bisects the distance between them. The fit is as good as might be expected when the condition of spread of small-pox in a large town is considered, and there is sufficient correspondence of the facts with the theory to make the interpretation given here at least probable.

As a general commentary on what has been said, it may be remarked in the first case that young children are more easily killed by certain organisms than older children. This susceptibility to death is related quantitatively to age, and this relation requires explanation. It may be explained if we assume that the young child has some substance present which affords a means of foothold to the attacking organism. This substance disappears with age in the manner of the mono-molecular chemical reaction. We then have a case of athreptic* immunity, that is, an immunity due to lack of nourishing substance in the attacked organisms.

The second and third cases may be considered together. As the death-

* Ehrlich's "atreptic" in the barbarous German spelling.

rate increases in a geometrical progression, it may be expected that some substance essential to vitality disappears in the organisms, according to the assumed law. In this way protection against fevers becomes more difficult with each year of age. So that the loss of immunity is due to the inability of the organisms to furnish protective substances. It is therefore distinct from case 1. With case 4 something essentially similar takes

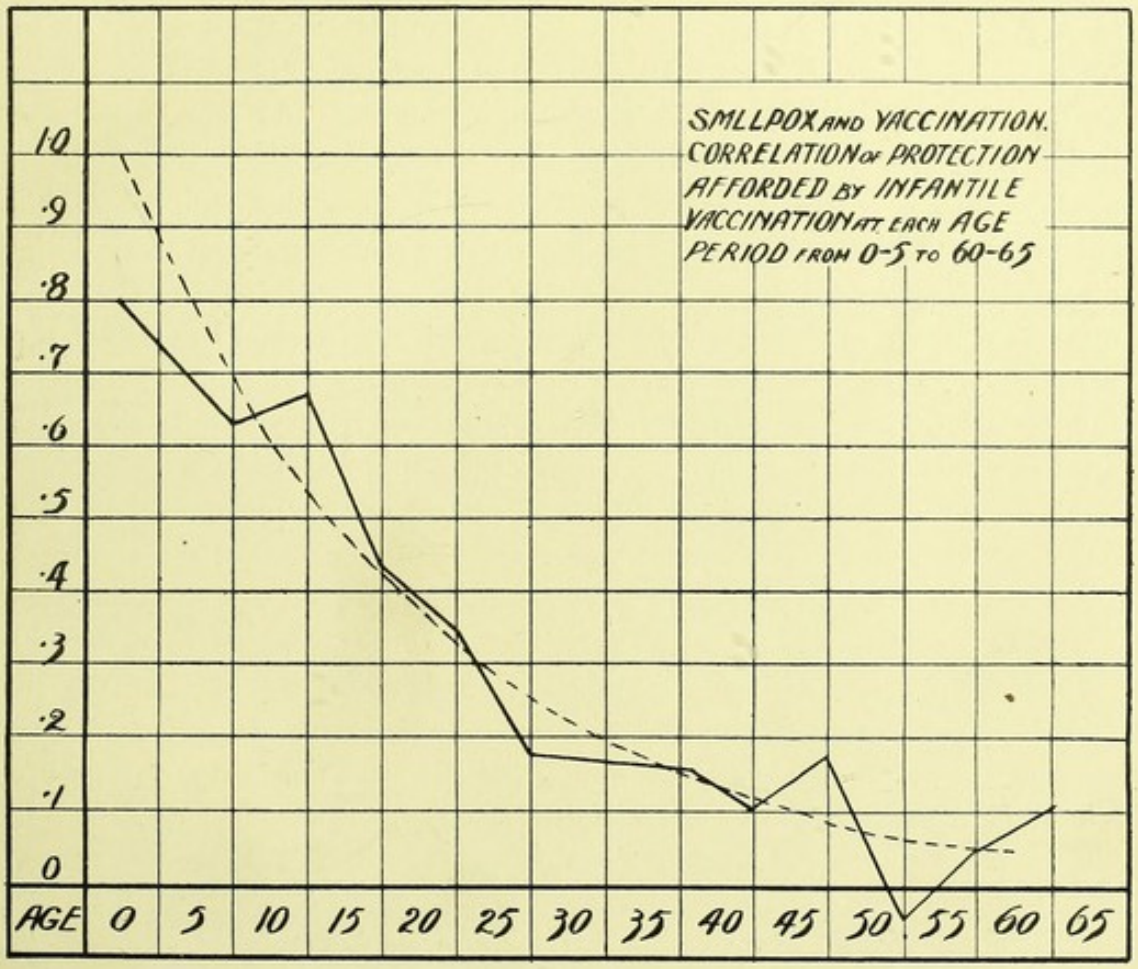

Diagram II.

place; the attacking organism in this case loses something necessary to the power of attack, and this lost, the epidemic terminates for the moment till by some means, possibly sexual, the vitality of the organism is regained. With some epidemic diseases this seems roughly cyclical. The fifth case is specially interesting as showing that acquired immunity passes in the same way, and that here also the substances in the body which control the reaction to disease behave essentially as if the loss of power were due to rearrangement of the various atoms of individual molecules.

Returning to Miss Chick's problem, the following remarks at once suggest themselves. In her paper the living organism is shown to act towards disinfectants as if it were itself a chemical substance. Thus the actual numbers of anthrax spores living after a specific period is in a geometrical progression. It is the same problem as if the whole population of a district were uniformly at the same instant exposed to an infective disease, and the uniform medium of infection kept constantly present in the same amount. In this case an epidemic curve would be, on her analogy, given by $y = ae^{-\beta t}$. In the cases here considered, however, it is some substance contained by the organism which is assumed to obey the mono-molecular law, and in each case a different kind of substance.

Her case is really in a different dimension from those given in this communication. She indeed touches on the general problem when she discusses the behaviour of *Bacillus paratyphosus*, and shows that the difference of age in the organism makes a great difference in the rate of the action. Thus the old organisms die more quickly than young, and thus the numbers living no longer obey the exponential law; but the data she gives are not sufficient to find the law of death even approximately.

I do not propose to carry this further at the present moment. The examples chosen are the chief obtainable. Those in case 2 are the most subject to criticism as selected. It is essential, however, that in this class we have equal freedom of infection, and that the disease be definitely infectious in a homogeneous population. Other diseases, such as enteric fever, do not seem to fulfil the conditions sufficiently. It can hardly be expected that the whole progress of immunity and mortality during life should be comprehended in one chemical law.

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