Table 1. Judgments of the brightest pair of flashes in a trio.

Subject	Interflash interval (msec)			N
	9	16	25	
	With filter			
E	76	23	9	108
H	72	32	4	108
L	175	35	6	216
S	67	29	12	108
	Without filter			
E	84	14	8	106
H	63	30	15	108
L	147	42	27	216
S	65	25	18	108

Table 2. Number of times (of 16 comparisons) the pairs of flashes with 9-msec interflash intervals produced amplitudes greater than those with 16-msec intervals.

Subject	Ordinate		Measured (sum of 10)
	120	210	
E	12	15	15
H	14	14	16
L	15	15	15

were obtained for each channel. (For example, if channels 1 and 3 were used for 9-msec separations and channels 2 and 4 for 16-msec separations, the recording sequence would be 1-2-4-3, repeated four times.) The computer stored and averaged the output of the Offner over the 0.5-second interval initiated by the first flash of each pair. Flash pairs followed one another at intervals of 1.1 seconds. Six to eight flash pairs were presented before each set was recorded. Four complete sessions as described were run with each subject.

The data for the first phase (Table 1) show that pairs of flashes with 9-msec interflash intervals were most frequently judged to be brightest, pairs with 25-msec interflash intervals were judged as brightest least frequently. Simple statistical tests (chi square) show the finding to be significant for each of the four subjects at each of the two luminances. Thus, although the subjects were "guessing," forced judgments indicate that the sensory response varied as a function of flash separation. For this method of stimulus presentation, wherein light is not continuously present for a given interval of time, Bloch's law seems to be valid only as a first approximation.

Figure 1 illustrates the nature of the differences in the evoked potentials obtained with the 9-msec and the 16-msec interflash intervals during a typical recording session. The two top tracings represent the 9-msec condition, while the two bottom tracings represent the 16-msec condition. Differences in the overall wave forms, representing differences in the relative amplitudes of the various components of the complex response pattern, are evident for the two conditions.

The records were analyzed by measuring amplitudes at certain points in time following the onset of stimulation. Three such indices of response amplitude were agreed upon before the experiment was performed, this choice being based on the results of previous studies in our laboratory in which flash luminance was varied systematically. One index was the trough-to-peak amplitude between the large negative peak at a latency of about 80 msec and the positive peak at about 120 msec; a second was the trough-to-peak amplitude for the positive peak at about 210 msec; and the third was the sum of the ordinates, again from the 80-msec trough as a baseline, as measured at 20-msec intervals from 60 to 240 msec. Thus the last was the sum of 10 ordinates specified by latency. Then each index was compared with the corresponding index for each of the two recordings of the evoked potential for the alternative interflash interval in the same block. Thus four comparisons were made in each of the four blocks for each subject. For most of the comparisons (Table 2), the pairs with the shorter interflash interval show the larger index. Application of the sign test shows that the differences found are statistically significant at a high level of confidence.

These findings, obtained with the average-response computer, attest to the power of this technique for studying the relation between neural and sensory events; it was necessary to employ what is probably the most sensitive psychophysical technique available in order to establish the relative brightness of the various fused flash pairs.

NEIL R. BARTLETT
University of Arizona, Tucson
CARROLL T. WHITE
U.S. Navy Electronics Laboratory, San Diego, California 92152

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15 February 1965

Some Kinetic Properties of a Deterministic Epidemic Confirmed by Computer Simulation

Abstract. *Representative epidemic transients were generated by computer by a known, plausible mechanism. Accurate retrieval of the individual rate constants and confirmation of their predictive value resulted from a manual test of the mechanism by which the computer outputs were generated. The method is applicable in principle to any regenerative process opposed by exponential decay.*

Muench (*1*) has discussed the applicability of certain deterministic models to epidemiology. His treatment deals, however, with the properties of an already established endemic steady-state, and not with the transient behavior that typifies the true epidemic. Muench's work, if read without proper attention to this distinction (*2*), can lead to the unrealistic conclusion that the rate of growth of an epidemic should be greatest at the moment of its birth.

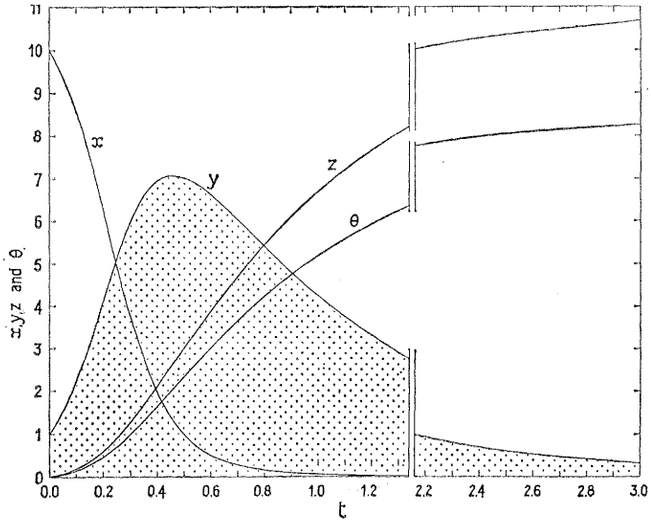
Bailey (*3*) has described a model that acknowledges the need for an autocatalytic component in the propagation of an epidemic outbreak, but incorporation of the opposing process of extinction required to account for its transience leads to a set of differential equations that appears not to have a general analytic solution. The approximation that Bailey presents is of little or no use as a mechanistic criterion, and probabilistic treatment of the same (*4*) or an even simpler (*5*) model leads to similar (*6*) and equally cumbersome results.

A test for consistency between the Bailey model and a given set of experimental data requires a method for calculating separate numerical values for the two specific rate constants for the processes of infection and recovery during a significant part of the duration of the epidemic. The same mechanism should, by definition, also be applicable to the dynamic behavior of other real systems whose parts likewise appear by self-replication (*7*) and disappear by 1st-order attrition (*8*); it seems desirable, for this reason, to describe here a simple, graphic method by which the required mechanistic test can be performed on suitable experimental data, and to assess the predictive usefulness of the resulting rate constants by analysis of a computer-simulated Bailey epidemic. The epidemiologic context

Table 1. Comparison of the properties found with the assigned or predicted properties of the computer-simulated epidemics shown in Figs. 1 to 4. The input values of k_1 and k_2 were chosen, after some exploratory runs with an analog computer (*24*), for their usefulness in illustrating certain points made in the text. Input assignments for x_0, y_0, z_0, and θ_0 are given in the legends to Figs. 1 to 4. The output values of x_m, y_m, z_m, θ_m, and t_m were read directly from the computer record to the nearest 0.02 in t. All remaining entries were derived by methods described in the text. The theoretical relevance of these methods to a real epidemic is indicated by the agreement between comparable entries in the table. (A, assigned; P, predicted; F, found.)

Fig.	k_1		k_2		x_m		y_m		z_m		θ_m		t_m		n	
	A	F	A	F	P	F	P	F	P	F	P	F	P	F	A	F*
1	1.000	0.998	1.290	1.289	1.29	1.27	7.07	7.07	2.64	2.66	2.05	2.06	0.47	0.46	11.00	11.00
2	1.200	1.197	1.550	1.551	1.29	1.31	7.07	7.06	2.64	2.63	1.70	1.69	0.39	0.38	11.00	11.00
3	1.000	0.998	2.000	2.000	2.00	2.01	5.78	5.78	3.22	3.21	1.61	1.62	0.44	0.44	11.00	11.00
4	1.000	0.998	5.000	5.000	5.00	4.99	2.54	2.53	3.46	3.48	0.69	0.70	0.36	0.36	11.00	11.00

* Invariant to 5 decimal places over the entire integration range.



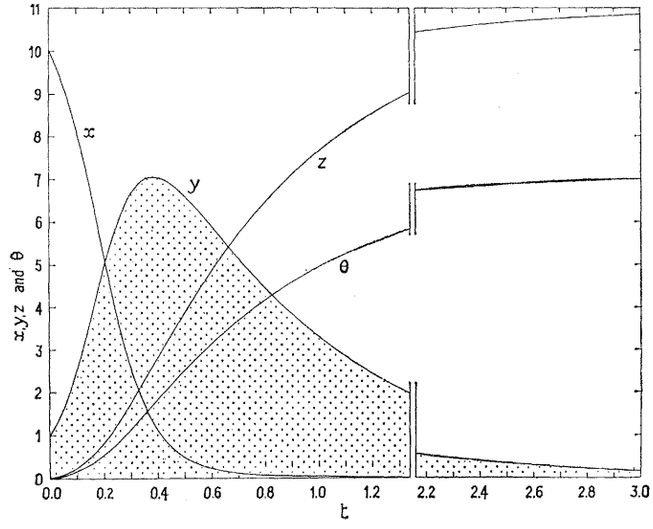
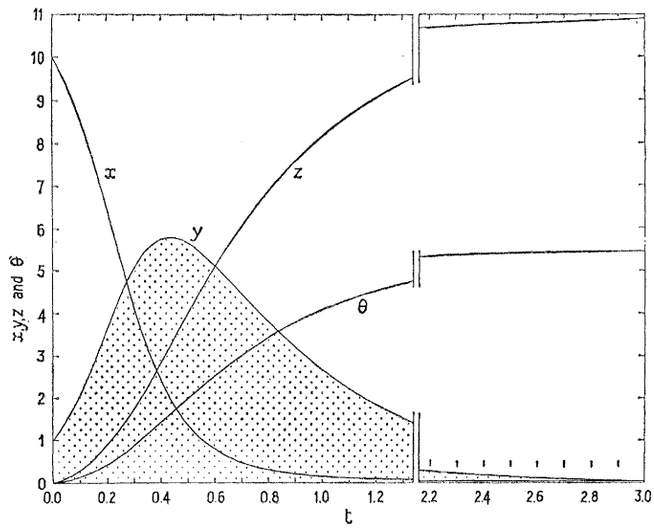


Fig. 1 (left). Analog version of the Bailey epidemic generated by computer from the input conditions: $k_1 = 1.000$; $k_2 = 1.290$; $x_0 = 10.00$; $y_0 = 1.00$; $z_0 = 0$; $\theta_0 = 0$. Fig. 2 (right). Analog version of the Bailey epidemic generated by computer from the input conditions: $k_1 = 1.200$; $k_2 = 1.550$; $x_0 = 10.00$; $y_0 = 1.00$; $z_0 = 0$; $\theta_0 = 0$.



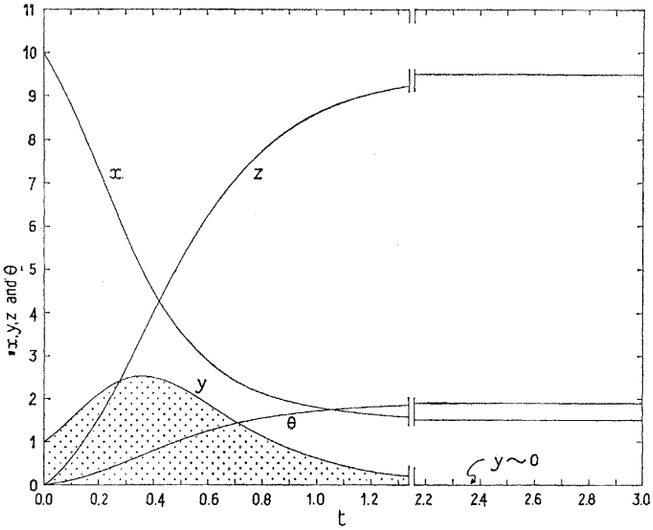


Fig. 3 (left). Analog version of the Bailey epidemic generated by computer from the input conditions: $k_1 = 1.000$; $k_2 = 2.000$; $x_0 = 10.00$; $y_0 = 1.00$; $z_0 = 0$; $\theta_0 = 0$. Fig. 4 (right). Analog version of the Bailey epidemic generated by computer from the input conditions: $k_1 = 1.000$; $k_2 = 5.000$; $x_0 = 10.00$; $y_0 = 1.00$; $z_0 = 0$; $\theta_0 = 0$.

will be retained in acknowledgment of the origin of the model, but the method should be equally relevant to chemical and to other biologic systems when their dynamics are controlled by the same mass action effects (*9*). The epidemic concept thus becomes a special case of the generalized birth-death process treated by Kendall (*10*) and by others (*6*, *11*).

Study of the Bailey mechanism,

$$X + Y \xrightarrow{k_1} 2Y \xrightarrow{k_2} 2Z$$

requires the following definitions:

n = a constant, representing total population density in a closed but freely intermingling population which occupies a locale of constant, unit size.
x = density of susceptible members, X, of the population in circulation at time t.
y = density of members, Y, of the population who, at time t, are in circulation and capable of transmitting the infection.
z = density of members, Z, of the population who are recovered and isolated, recovered and immune, or dead at time t. The model does not distinguish among these possible fates for Y, but requires only that the step, Y → Z, shall represent net 1st-order removal of subjects from the susceptible-infectious pool by one or more such processes.
x_0, y_0, and z_0 = values of the respective variables at $t = 0$.
k_1 = specific rate constant for the infectious process: a composite measure of the rate of successful exposure and the incubation period.
k_2 = specific rate constant for the recovery process: an inverse measure of the duration of the disease. When the step, Y → Z, represents collectively both death and recovery, then k_2 will represent the sum of the rate constants for the individual processes.

The first step is autocatalytic and the second step is 1st-order, so the relevant rate equations are:

$$dx/dt = -k_1xy \quad (1)$$
$$dy/dt = k_1xy - k_2y \quad (2)$$
$$dz/dt = k_2y \quad (3)$$

Since the population is closed, a supplementary conservation equation,

$$x + y + z = n \quad (4)$$

will also apply.

The autocatalytic feature by which this model differs from the endemic propagation model of Muench appears (*12*) as positive feedback, y, in the k_1xy term of Eqs. 1 and 2. Extension of the Bailey mechanism to chemical or to other kinds of biologic self-replication would consider Y the template, formed autocatalytically from species X and converted to Z by any 1st-order process whatever.

At least one infectious unit, Y, is required to trigger the epidemic, so the earliest permissible boundary conditions are, in terms consistent with Eq. 4,

$$x_0 = n - 1 \quad (5)$$
$$y_0 = 1 \quad (6)$$
$$z_0 = 0 \quad (7)$$

In practice, of course, an epidemic is never detected as soon as implied by Eqs. 5 to 7, and other, more realistic initial conditions will, in fact, always prevail. The results to follow will apply when the initial conditions refer to any belated point, $t_0 > 0$, after the epidemic is known to have begun; it will be more instructive, however, to emphasize here the ideal case when $t_0 = 0$, since the expected early lag in infection rate will then be more clearly evident.

Solution of Eqs. 1 to 3 is complicated by their nonlinearity and, for this reason, Bailey had to assume that $z <<< k_2/k_1$ as a means of performing one of the necessary integrations. This assumption is valid only during the earliest stage of epidemic spread or for epidemics of the mildest sort, but, even if granted, the resulting approximation has little diagnostic value. This difficulty can be avoided, however, by introducing a simplifying parameter, θ, defined by French (*13*) and by Wideqvist (*14*) as follows:

$$\theta = \int_0^t y \, dt \quad (8)$$

The practical value of the θ-function as a device for integrating Eqs. 1 to 3 lies not only in the ease and sufficient accuracy with which it can be evaluated graphically, but also in its simplicity as a measure of the cumulative "man-hours" of infection already spread by the process by time, t. The fuller significance of the θ-function as a means of characterizing this process will be apparent later.

Differentiation of Eq. 8 gives,

$$d\theta/dt = y \quad (9)$$

and substitution of Eq. 9 into Eqs. 1 to 3 gives,

$$dx/d\theta = -k_1x \quad (10)$$
$$dy/d\theta = k_1x - k_2 \quad (11)$$
$$dz/d\theta = k_2 \quad (12)$$

Introduction of the θ-function has, in effect, reduced by one the number of variables in the problem, and Eqs. 10 to 12, by contrast with Eqs. 1 to 3, can now be integrated. Integration of Eqs. 10 and 12 is sufficient, since y is always available from Eq. 4 by difference. The results,

$$\ln x = -k_1\theta + \ln x_0 \quad (13)$$

and

$$z = k_2\theta + z_0 \quad (14)$$

are linear, so numerical values for k_1 and k_2 can now be determined as follows.

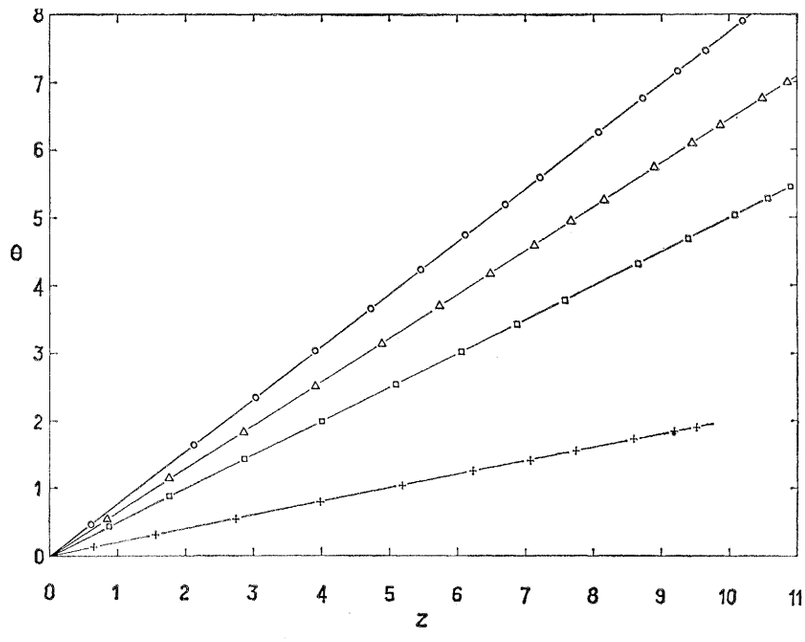
1) Graphic integration of a plot of y versus t from $t = 0$ to various values of t gives, as specified by Eq. 8, a series of values for θ. Since θ is a *cumulative* function of time, it will be most meaningful when the initial time to which it refers is clearly identifiable as the beginning of epidemic spread. When this is not possible, resort to the extrapolation method discussed by Bak (*15*) may be useful.

2) A plot of these successive values of θ against synchronous values of z gives a line whose slope is k_2, as required by Eq. 14. Dimensional analysis (*16*) of Eq. 3 shows that k_2 has the dimension, *recoveries or deaths (or both) per unit time*.

3) The same values of θ plotted against synchronous values of decadic log x gives a line whose slope is as required by Eq. 13, $-k_1/2.303$. The dimensions of k_1 are *effective contacts per person per unit time*, evident from a dimensional study (*16*) of Eq. 1.

Linearity or nonlinearity of the resulting plots then indicates that the composite process does or does not, in fact, occur by the proposed mechanism. Bailey's presentation, by contrast, permits at most a calculation of the ratio, k_2/k_1, with less-committal mechanistic insight than provided by a knowledge of k_1 and k_2 separately. When the model truly applies, the values of k_1 and k_2 will become unique determinants of the course of the epidemic, and will represent, in a kinetic sense, the only possible distinction between one kind of epidemic and another. Some of the predictive properties of these constants, once obtained for a particular kind of epidemic, will be referred to later in this report.

The foregoing solution of Eqs. 1 to 3 in terms of θ is still only a partial solution, since it does not define explicitly the time-dependence of the variables. This dependence can be depicted accurately and with ease, however, by computer simulation. The re-



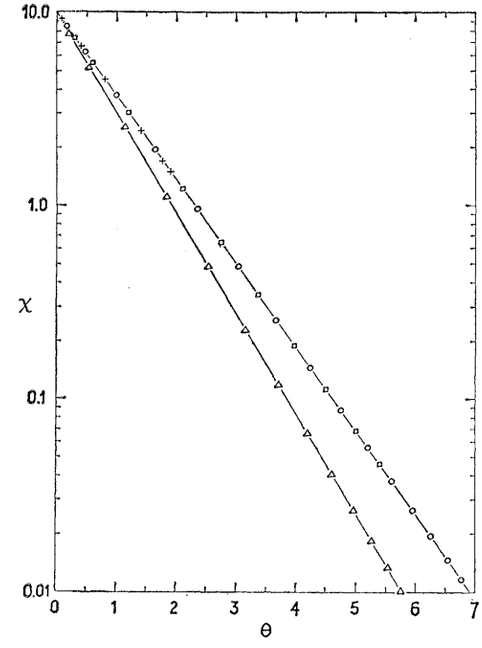


Fig. 5 (left). Plots of θ versus z corresponding to Figs. 1 (circles), 2 (triangles), 3 (squares), 4 (crosses). Fig. 6 (right). Plots of θ versus log x corresponding to Figs. 1 (circles), 2 (triangles), 3 (squares), and 4 (crosses).

sulting "epidemic" will have "occurred" by a known mechanism at a known rate and will therefore serve as a means for testing the methods in question, including some which are discussed below. The results will, in addition, be amenable to direct comparison with actual epidemiologic data.

Figures 1 to 4 represent smoothed digital simulations of this kind, accomplished by use of the University of London Atlas computer programmed for solution of Eqs. 1 to 3 and Eq. 8 in terms of the four particular sets of input conditions quoted in the legends for the figures. Input values of x_0, k_1, and k_2 were in each case chosen such that $x_0 > k_2/k_1$, as required before an epidemic can occur (*3*, ch. 4). The further stipulations, $x_0 >> y_0 > 0$, $\theta_0 = 0$, and $z_0 = 0$, served to prime the infectious process and to assure representation of its course before, as well as during and after, its peak.

The computer program was written for 4th-order Runge-Kutta solutions (*17*) of Eqs. 1 to 3 and Eq. 8 with a constant step-length of 0.02 in t. Computer summation of x, y, and z at each time increment gave, by Eq. 4, corresponding values for n, and the constancy of these values to five decimal places over the entire integration range gave assurance that rounding errors did not accumulate during the stepwise solution. Each solution was then repeated with a constant step-length of 0.05 in t in order to provide an indication of the magnitude of truncation errors. Since the truncation error introduced by the Runge-Kutta method is proportional to the 5th-power of the step-length, the errors in the integration for $\triangle t = 0.02$ should be $(0.02/0.05)^5 \sim 0.01$ as large as those with $\triangle t = 0.05$. The largest discrepancy noted between the computer print-outs for the duplicate solutions is about 6 units in the fourth decimal place, so the solution at the smaller step-length should be correct to about 6 units in the sixth decimal place. An error of this size is, of course, far less than the graphing errors inherent in the manual construction of Figs. 1 to 6 from the computer log.

Theoretical correctness of the present mechanistic test is evidenced by linearity of the correlations appearing in Figs. 5 and 6, obtained by application of graphic steps 1 to 3 to each of the computer outputs shown in analog form in Figs. 1 to 4. An indication of the computational accuracy of the method is seen in Table 1, where the assigned computer input values for k_1 and k_2 are compared with those retrieved by application of manual steps 1 to 3 to Figs. 1 to 4.

The changes described by Figs. 1 to 4 are, of course, fictional in the sense that x, y, z, and θ will always be integer-valued functions of time; the continuity implied by these figures will, thus, be approached only when the population is much larger than the one chosen here. The illustrative purpose of Figs. 1 to 4 is, however, unaffected: Fig. 4 shows, for example, that the model is realistic in permitting the demise of a *mild* epidemic without affecting all susceptibles. Figure 1 illustrates, by contrast, the possible persistence of infection long after the susceptible pool has been dried-up by a more severe outbreak. Further comparison of Figs. 1 to 4 shows that two equally severe epidemics may peak at different times (Figs. 1 and 2), while two epidemics that peak at the same time may differ in severity (Figs. 1 and 3; 2 and 4). The obvious dependence of these effects on the relative magnitudes of k_1 and k_2 has been simplified, in the four cases illustrated, by deliberately holding constant the relative inoculum size, y_0/x_0. The nature of this dependence can then be established by solving Eqs. 1 to 3 and Eq. 8 for the properties of the epidemic at the time of its peak.

The point, y_m, corresponding to the inflection in the y-trace, can be identified algebraically by first setting $dy/dt = 0$ in Eq. 2: the immediate result,

$$x_m = k_2/k_1 \qquad (15)$$

which defines a synchronous point on the x-trace, now makes clear the requirement stated earlier that x_0 be $> k_2/k_1$ before an epidemic can occur. Integration of the quotient of Eqs. 1 and 3 and substitution of Eq. 15 into the result yields

$$z_m = 2.303\, x_m \log (x_0/x_m) \qquad (16)$$

for the associated value of z. The required value for y_m then results, by difference, from the relationship

$$y_m = n - (x_m + z_m) \qquad (17)$$

The predicted value for the corresponding point, θ_m, on the θ-trace results, of course, from replacing z in Eq. 14 with the value of z_m calculated by use of Eq. 16. The quantity θ_m, representing the integrated amount of infection spread by the process during the period $t_0 \rightarrow t_m$, has both a time and intensity dimension and may thus be taken as a more meaningful definition of *epidemic severity* (*18*) than is offered by y_m alone. Note in Table 1, for example, that Figs. 1 and 2 represent epidemics of equal peak intensity (y_m) but obviously different severities (θ_m).

When $z_m << x_m$, an approximate value for the time-of-occurrence of the epidemic peak, t_m, is available—though with difficulty—by substituting z_m into Bailey's result (*3*) for z as a function of t. None of the epidemics represented in Figs. 1 to 4 is mild enough to meet this condition. A much simpler and more general expression for t_m is obtained by rewriting Eq. 8 in terms of the Euler-Maclaurin summation formula (*19*). The result,

$$\theta = \int_0^t y\, dt = \frac{(y_0 + y)}{2}\, t - \frac{(dy/dt - [dy/dt]_0)}{12}\, t^2 + \frac{(d^3y/dt^3 - [d^3y/dt^3]_0)}{720}\, t^4 - \ldots . \text{etc.} \qquad (18)$$

reduces to the quadratic equation

$$\theta = \frac{(y_0 + y)}{2}\, t - \frac{(dy/dt - [dy/dt]_0)}{12}\, t^2 \qquad (19)$$

by ignoring terms beyond the second. When $t = t_m$, y becomes y_m, $\theta = \theta_m$, $dy/dt = (dy/dt)_m = 0$, and Eq. 19 becomes

$$\theta_m = \frac{(y_0 + y_m)}{2}\, t_m + \frac{(dy/dt)_0}{12}\, t^2_m \qquad (20)$$

The value of dy/dt at any time is defined by Eq. 2, so at t_0,

$$(dy/dt)_0 = k_1x_0y_0 - k_2y_0 \qquad (21)$$

which converts Eq. 20 to

$$\theta_m = \frac{(y_0 + y_m)}{2}\, t_m + \frac{(k_1x_0y_0 - k_2y_0)}{12}\, t^2_m \qquad (22)$$

Solution of this quadratic equation yields the desired value of t_m. The predicted values of t_m shown in Table 1 were obtained in this way: their agreement with the derived values appearing there confirms further the predictability of several of the significant properties of a future epidemic from a prior knowledge of k_1 and k_2, obtained by the graphic procedure already discussed. The ratio, k_2/k_1, provided by Bailey's treatment is useless for this purpose because of the dependence of t_m upon a knowledge of k_1 and k_2 separately, as shown by the form of the right-most coefficient in Eq. 22.

The appeal of the Bailey model, as applied to epidemiology in the strict sense, is qualified (*3*, pp. 172–175; *6*, p. 168) by the failure of real, macroscopic populations to behave in a fully deterministic manner—as a "two-dimensional ideal gas," to paraphrase Muench. Its credibility is nevertheless suggested by the basic similarity of the x- and y-traces in Figs. 1 to 4 to those found experimentally (*20*). The objection is further tempered by the versatility with which the model can account for the early accelerative phase of epidemic growth seen both in induced (*20*) and in spontaneous (*21*) epidemics. The relative prominence of this feature, exemplified by the early part of the y-traces in Figs. 1 to 4, is obviously related to k_2/k_1.

It will be even more sensitive to changes in the initial makeup of the population (y_0/x_0), but, however faintly discernible, it will always be inherently present. The relevance of the analytic methods described here to a real epidemic thus seems acceptable as a heuristic approach to reality, and the expected scatter in the raw data will simply require the application of suitable linear regression methods (*22*) when experimental analogs of Figs. 5 and 6 are constructed. When computer facilities are available, an iteration method recently described by Gay (*23*) will be preferable since it will provide statistically correct values of k_1 and k_2 from imprecise data by reversal of the procedure used here to obtain Figs. 1 to 4.

MARTIN L. BLACK
Research Laboratories,
Parke, Davis and Company,
Ann Arbor, Michigan

IAN D. GAY*
Department of Chemistry,
Imperial College of Science
and Technology, London, S.W.7

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* Present address: Department of Chemistry, Harvard University, Cambridge, Mass. 02138.

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