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THE INCUBATION PERIOD AND THE DYNAMICS OF INFECTIOUS DISEASE

By

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The course of epidemics is a central characteristic of infectious processes, which has been studied by three main approaches: observational, experimental, and mathematical or theoretical. Especially in the third of these methods, it is believed that the incubation period and a related temporal factor, the generation time, have received insufficient attention. Most of the epidemic models that have been constructed, for example, do not deal with discrete time intervals corresponding to the natural behavior of infectious disease. The Reed-Frost model as applied to observed epidemics by Abbey (1) and as modified to meet various conditions by Maia (2), is an exception to this statement. Bailey (3) has developed deterministic models and much more elaborate stochastic models for epidemics, and has also made estimates of the latent period and period of infectivity.

Much of the previous work on epidemic theory, however, might have been facilitated by a more clear appreciation of the dynamics of infectious disease and how this is influenced by the incubation period. An early example of this was afforded by Brownlee's hypothesis that the declining phase of an epidemic, whether of the propagated or common-vehicle sort, was a result of the loss of infectivity of the etiological agent (4). He presented the epidemic curves of two outbreaks of scarlet fever in Wimbledon and Glasgow, which lasted about 10 days and were attributed to milk as a vehicle. He wrote, "In these it will be noted that the loss of infectivity has been especially rapid; and though a large amount of infection has been thrown into the milk, yet when it is observed that the incubation period of scarlet fever is from three to five days, it can be seen that at the time the milk supply was stopped, the organism had in both instances run almost the complete cycle of its infectivity." We would today explain the time curves in these outbreaks as due to the variation in incubation period plus the period over which the milk was consumed and the diminishing number of susceptibles remaining available for attack after the first days.

An even more obvious error was found in a report of a British milk-borne outbreak of 518 cases of typhoid, of which all but 7 occurred within a span of 38 days. The investigator stated that the incubation period of this disease was about 12 to 14 days, the limits rarely lying outside 7 to 17 days. He assumed for the purpose of his inquiry an incubation period of 14 days, and concluded that the milk was infective continuously for a period of three to four weeks (elsewhere stated as a period of 31 days or

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thereabouts). From this premise it would be reasonable to conclude that the cows were actively infected and excreting typhoid bacilli in their milk, but it is highly probable that the milk from only one day's milking was contaminated from a human source during or after milking and the observed spread of cases was due almost entirely to the natural variation in incubation periods, with some slight contribution from variation in the date of ingestion and possibly a few secondary cases. Ranges in the incubation period of typhoid of as much as one month have repeatedly been noted.

Thus there are a number of reasons why a better understanding of the dynamics of disease can be helpful in understanding epidemic phenomena; and the dynamics of disease is closely related to incubation periods.

In two earlier reports (5, 6) it was shown that incubation periods of many diseases were distributed in an approximately logarithmic-normal fashion. A graphic method was described for judging whether a particular set of values conformed to this distribution and for estimating the two parameters, the median and dispersion factor (antilogarithm of logarithmic standard deviation). The similarity in dispersion factors of incubation periods of diseases with widely varying median values was stressed.

Several workers have since made use of these properties. It is the purpose of this paper to summarize some of the uses to which a knowledge of incubation times may be put, drawing upon these subsequent papers and additional information secured since publication of the earlier studies.

A further note on the curve-fitting technique beyond that given previously (5) is perhaps needed. The estimation of the character of the curve and of the parameters is secured by plotting cumulative percentages of the grouped data against the logarithm of time on probability paper. Each cumulative percentage point is plotted to the beginning of the next succeeding time interval. Probability paper having a scale from 1 per cent to 99 per cent (Codex no. 32,451) is used. A straight line is fitted by inspection and the log times corresponding to the intersection of the line with the 16 percentile, 50 percentile and 84 percentile rulings are recorded. The 50 percentile is transformed back to the original time units. This value, termed the estimated median, does not correspond exactly to the median as determined by arithmetic interpolation between the two values adjacent to the median, because it is obtained from probability paper, and because a number of points along the slope are considered in fitting the line. The estimated median is considered a better estimate of the true value than the arithmetically interpolated median. The slope of the line is measured by taking the distance on the log-time axis between the 16th and 84th percentile points, which corresponds roughly to two standard deviations, and dividing by two. The antilogarithm of this quantity, termed the dispersion factor, increases as the variation in incubation periods becomes larger. A dispersion factor of 1 signifies that there is no variation; a dispersion factor of 1.5 means that a range from 0.44 times the median (median $\div 1.5^2$) to 2.25 times the median (median $\times 1.5^2$) encompasses about 95 per cent of the distribution.

Exact values of these parameters can, of course, be calculated by arithmetic methods, as the geometric mean and standard deviation. The graphic method,

TABLE 1

Parameters of additional incubation period distributions, approximately log-normal in shape

	Number of cases in series	Estimated median (days)	Dispersion factor
Syphilis in rabbit (after inoculation of 500 treponemes) (19)	106	17.6	1.12
Mumps (13)	54	19.5	1.12
Chickenpox (20)	127	14.0	1.14
Smallpox by inoculation (12)	310	13.0	1.13
CNS illness after smallpox vaccination (21)	64	10.0	1.46
CNS illness after 17D yellow fever vaccination (Group 3) (22)	55	12.2	1.31
Tetanus—from date of injury			
Series of Spaeth (23)	223	9.1	1.68
Series of Tateno (17)			
Head and face injuries	24	8.5	1.75
Lower leg injuries	95	11.0	1.68
All cases, including the above and others	157	10.4	1.67

however, is fairly reproducible and, when the distribution is satisfactory, yields parameters reasonably close to the true values. A graphic depiction of the distribution is desirable in any case, in order to determine its character. Values at the ends of the distribution should receive less weight in curve-fitting. The data are rarely sufficiently accurate to justify more elaborate methods of analysis.

Data have been presented (5) from 18 studies of 13 diseases in which the distributions were approximately log-normal, and the parameters were calculated. These will not be repeated here. Study of many distributions found in the literature since the earlier publication has confirmed the statements made at that time and emphasized the utility of the method. Eight further examples, selected either to illustrate points made in this paper or because the accuracy of the observations is presumed to be quite good or the number of observations is large, are furnished in table 1. All of the observations, both in this and the preceding papers, are drawn from the medical literature rather than from the author's experience and may be presumed to be free of preconceptions as to the probable shape of the distributions.

Dispersion factors are remarkably similar in different reported series of cases of a specific disease. They do not show any consistent relationship with length of incubation period, being low as frequently for diseases of prolonged incubation time as for diseases of short incubation time. Small dispersion factors of less than 1.2 indicating little variation around the median, are found in chickenpox, smallpox, mumps and measles; all these are virus diseases in which inapparent infections are infrequent. At the other extreme are amebic dysentery, tetanus and some other bacterial and protozoal infections or intoxications, which have large dispersion factors.

The data on serum hepatitis might appear to be more reliably determinable than most incubation periods. This is not the case for transfused persons, since they may receive multiple transfusions at different times and one then does not know which transfusion to blame. Some workers have dated incubation periods from the earliest, some from the latest transfusion. Also, some patients are bound to be lost to observation over the long incubation period and others die of the disease for which the transfusion was administered, who might otherwise have been destined to come down with jaundice. Neverthe-

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TABLE 2

Incubation periods of serum hepatitis

	No. of subjects	Med.	Disp. factor	Note
A. Following administration of early yellow fever vaccines which contained human serum				
Sawyer et al. (24)	5914	100	1.24	
Findlay et al. (25)	707	105	1.27	
Fox et al. (22)	730	128	1.23	Lot 489 (cases through 30 weeks)
B. Following administration of blood or blood products for therapeutic purposes				
Spurling et al. (26)	77	76.6	1.39	Limited to those with onset within five months
Allen et al. (27)	113	63.4	1.71	
Duncan et al. (28)	23	83.2	1.29	Controls for study of gamma globulin
Murphy et al. (29)	23	86.3	1.41	Irradiated plasma
Brightman et al. (30)	29	84.1	1.39	Pooled dried plasma

less it is of interest to examine table 2 which provides data from three series which followed administration of early lots of yellow fever vaccine containing human serum as a preservative, and five series in which blood or blood products were administered therapeutically. In the former, median incubation periods were uniformly longer (100 to 128 days) than the latter (63 to 86 days), and the dispersion factors uniformly smaller (1.23 to 1.27 as compared with 1.29 to 1.71). The most reasonable explanation appears to be that in the former situation the dosage of serum hepatitis virus was smaller and more uniform than in the latter. It must be admitted, however, that deaths within the first six months after transfusion, and before having manifested evidence of hepatitis, would tend to bias the recorded incubation periods of patients given blood for therapeutic purposes in the direction observed.

Several instances have also been found in which the distribution did not conform to a log-normal curve. The most common departure was a greater skewness than that which is correctible by transformation of the times to a log scale, i.e., a longer tail to the right-hand end of the distribution. No attempt has been made to find an appropriate transformation for these curves. Several of these excessively skewed distributions were derived from experimental animal data in which the route of inoculation was artificial (e.g., intravenous or intracerebral). In such cases average incubation times are regularly shortened in animal experiments by comparison with the natural route of infection. There was also a human experimental series in which the distribution was far from log normal. In the series of 82 intraurethral inoculations of gonococci in experimental human subjects by Mahoney and associates (7), over 80 per cent of onsets occurred within 6 days but the remainder extended to a maximum of 31 days, resulting in an excessively skewed distribution.

TABLE 3

Ranges of observations around the median, taken as unity, encompassed by specified percentiles, for three values of the dispersion factor

Dispersion factor	25%–75% (50% of total)	16%–84% (68% of total)	2.5%–97.5% (95% of total)
1.2	.88–1.13	.83–1.20	.69–1.44
1.4	.79–1.26	.71–1.40	.51–1.96
1.6	.73–1.38	.62–1.60	.39–2.56

Oki (8) suggests that "the distribution type of the incubation period is more legitimately considered to be non-central log-normal, . . . though a usual log-normal distribution may well be used. . . ." He points out that dispersion factors derived by the non-central (three-parameter) log-normal model are larger than those derived by a usual (two-parameter) log-normal model, and concentrate more closely around 1.5. He lists 9 diseases in which the log-normal distribution was appropriate, and 3 in which his non-central model gave a better approximation (measles, serum hepatitis, and typhoid fever). Although Oki's method may provide a better fit in some instances, the original method has continued to be employed because it is simpler and is adequate for most situations.

Some uses of a knowledge of incubation period will be discussed in the remainder of this paper, under four headings: judging the dynamics of an epidemic; estimation of the date of a common exposure; determination of the time of maximum infectiousness (the generation time); and contributing to the understanding of pathogenesis.

1. Judging the dynamics of an epidemic. An epidemic of a disease which can be transmitted either by a common vehicle or from person to person (such as streptococcal pharyngitis and infectious hepatitis) may represent three possible situations. It may have resulted from nearly simultaneous exposure of a large number of persons to a common vehicle, as when a contaminated food is served at a common gathering; from protracted exposure to the common vehicle, as when a milk supply contains streptococci, shed by a cow with mastitis, over a period of weeks; or from propagation of the infectious agent from person to person.

The distinction between the first and third of these alternatives is usually fairly easy, since in the third case the range of onsets will be several times the maximum range of incubation periods. The distinction between the first and second may present greater difficulty. A knowledge of the parameters discussed in this paper is helpful in deciding whether or not an epidemic can most rationally be explained on the basis of nearly simultaneous exposures of a group to the infectious agent, provided that these parameters are known or can be roughly estimated.

In a single-exposure, common-vehicle epidemic the range of onset dates around the median should not exceed certain values. Table 3 indicates the percentile ranges encompassed by diseases having different dispersion factors. To give an idea of how this could be used, suppose that we have an outbreak of streptococcal sore throat. From published data (5) we may estimate the median incubation period as 2.5 days and the dispersion factor as 1.5. Reference to table 3 shows that with dispersion factor 1.6 the range of the central 68 per cent of cases (from the 16th to the 84th percentile) should be from about 0.6 times the median (or 1.5 days) to 1.6 times the median (or 4 days), a span

of not over 3 days. Therefore, if substantially more than 30 per cent of onsets fall outside the central 3-day span it may be presumed that exposure of the population at risk was continued over several days. This of course requires that onset dates be accurately known (dates of report are no substitute) and that unrelated or secondary streptococcal infections are not included in sufficient numbers to be disturbing.

2. Estimation of date of common exposure. It occasionally happens that a group of subjects can be assumed to have been exposed to infection at a common time, but that time is not known. For instance, in an institutional outbreak it may be known that some meal was responsible for a mass outbreak of an intestinal infection but not which meal.

In such situations, on the assumption that the distribution is a two-parameter log-normal one, it is theoretically possible to estimate the time of common exposure. There are several mathematical methods for doing this, of which the simplest is the method of quantiles. This assumes the relationship $a = (b_1b_3 - b_2^2)/(b_1 + b_3 - 2b_2)$ where a is the date of common exposure, b_2 is the median date of onset, and b_1 and b_3 are selected, symmetrical points on the curve of onsets. For example, b_1 may be the date of the 25th percentile case, b_2 the date of the 50th percentile case, and b_3 that of the 75th percentile case. According to Aitchison and Brown (9), the most efficient pair of points to take for estimation of a, are the 27th and 73rd percentiles. In practice, the calendar dates of the three percentiles may have a constant added to them so that a will be a positive integer. Thus if the 25th and 75th percentiles fall on July 2, 6 and 12 these numbers may be changed to 10, 14 and 20; $a = (10)(20) - 14^2 / 10 + 20 - 2(14) = 2$ on the new scale, or June 24 on the calendar time scale.

TABLE 4

Attempts to estimate time of exposure from percentile points of epidemic curve, where actual time of exposure was known

Epidemic	No. of cases	Estimated time of exposure in relation to actual time
Staphylococcal food poisoning (31)	144	One hour early, or one hour late, depending on whether b_1 and b_2 taken as 10 and 90 percentile points, or 25 and 75 percentile points.
Bacillary dysentery (32)	97	One-half day late
Streptococcal sore throat (33)	113	One-half day late
Streptococcal sore throat (34)	98	Identical
Salmonellosis (35)	227	One-half or one day late, depending on whether b_1 and b_2 taken as 10 and 90 percentile points, or 20 and 80 percentile points.

This method has been tried in a number of cases where the time of common exposure was known, to see how well this time could be estimated. As table 4 shows, the method was capable of approximating the exposure time but not with sufficient reliability to be very useful except in one of the outbreaks studied. It seems doubtful that any better approximation can be achieved by this method, for diseases in which the average incubation period is reasonably well known, than by merely subtracting the mean incubation period from the mean of the epidemic curve. However, further work on this problem by more refined

TABLE 5

Intervals involved in estimation of incubation period and generation time in mumps, after Meyer (13) generation time

	No. of cases on which based	Median (days)	Disp. factor
Interval between a single exposure and onset of disease in contacts	54	19.5	1.12
Interval between onset of primary and secondary cases in families	127	18.3	1.15
Interval between onset of primary and secondary cases in schools	99	18.0	1.13

statistical methods should be encouraged. Results should be best when the series is large, conforms closely to a log-normal distribution, and of course, when the onset times have been very carefully established. The method can give meaningful results only when all the individuals in the epidemic were exposed at almost precisely the same time. A rough test of whether this was the situation is to take the difference between the times of onset of the first and last cases and see whether this interval exceeds the limits of incubation time as given in such compendia as "The Control of Communicable Diseases in Man" (10).

Hill (11) has used another, more complex method to estimate the time of exposure. He employs a Bayesian analysis based on the assumption, taken from (5), that incubation periods are log-normally distributed. It has the advantage of indicating the degree of accuracy of the estimate. Hill applied it to a tabulation of 310 smallpox cases reported by Haygarth (12) resulting from inoculation of susceptible persons with variolous matter in the 18th century. Hill's estimate of the day of inoculation was between one and two days in error, but the true value fell well within the limits that he estimated to have 95 per cent probability of including the true value.

3. Determination of time of maximum infectiousness of source case; relationship to "generation time." In studies of the familial distribution of acute contagious disease, the time of occurrence of secondary cases is governed by two factors: the time (in relation to the onset of clinical symptoms) at which the source case passed the infection to his contacts; and the incubation period. Both these times can vary.

It is sometimes tacitly assumed that the time of greatest infectiousness of the acute contagious diseases corresponds precisely to the end of incubation and onset of disease, or that infectiousness extends from several days before to several days after the onset of symptoms, being equally great throughout this range. Neither assumption is necessarily correct. While microbiological studies are capable of shedding much light on this, we should seek direct epidemiologic evidence as well.

Table 5 consists of data from a study of mumps by Meyer (13), who determined onset times (taken as the day on which salivary gland swelling was first noted) in relation to prior exposure. An estimate of incubation periods was secured in 54 instances where exposure was limited to one day, and this estimate (19.5 days) agrees well with estimates from other sources. The interval between onsets of primary and secondary cases after school and family exposures was also determined; these two estimates (18.0 and 18.3) do not differ significantly from each other but are significantly shorter than the incubation period estimate. Their dispersion

factors are but little larger than that of the incubation period.

These two observations, taken together, suggest that infection was usually transmitted on the day before clinical onset in the source case. Since the source case was removed from school as soon as parotid swelling was noted, the child could not infect his schoolmates after that date, but in the case of household exposure this limitation often does not apply. Were infectivity in fact present over the considerable span of time during which mumps virus has been detected in saliva, one would not expect to find the secondary crop of cases as limited in their period of onset as was the case in this and other studies.

The interval between receipt of infection by a susceptible, and the time when he is most likely to transmit it to others, deserves to be recognized as an epidemiologic concept. The term suggested here for it is the generation time. Hope Simpson (14) in 1948 termed it the serial interval.

An objection to the concept of a generation time is that it implies that the period of transmissibility of an infectious agent is very brief when, in fact, it is not. There is great variation in the duration of infectivity of hosts infected with different agents. In tuberculosis, syphilis, yaws and a number of intestinal parasitic infections, for example, there is often a period of months or years, during which the individual is infectious either continuously or intermittently. On the other hand, in most of the acute viral contagious diseases—measles, German measles, mumps and chickenpox, in particular—the epidemiologic pattern is such as to suggest strongly that the infectious period is very brief, a matter of a few days at most. The evidence for this statement is found in the many instances in residential schools and institutions, in which successive discrete clusters of cases can be clearly identified over 5 or more disease generations, as well as in the composite curve of secondary household cases.

There is some discrepancy in this regard between epidemiologic and microbiologic evidence. In mumps, for example, the virus has been detected in saliva from 5 days before onset to 4 days after onset. It is nevertheless probable that the titer of virus or the probability of excretion of virus may fall off so greatly as one moves away from the central day of infectivity, that significant infectivity is limited to a short period. Even in diseases where infectivity is of long duration it is proper to refer to a generation time as the average interval which elapses between receipt and transmission of infection, although in such diseases successive cases in the chain would not be clustered.

The fact that the generation time, rather than the incubation period, is the determinant of the dynamics of spread, was clearly pointed out by Hope Simpson but has perhaps been disregarded because the generation time and incubation period are nearly identical in most of the acute contagious diseases. There are, however, some diseases in which they do not coincide—for instance, syphilis, in which the generation time is longer than the incubation period. Furthermore, it is only the generation time that can be measured in the case of inapparent infections; and the precision of thinking is greater when this distinction is made.

Figure 1, data for which were kindly provided by Dr. George W. Comstock, represents the flow of mumps through Mt. Edgecumbe High School, a residen-

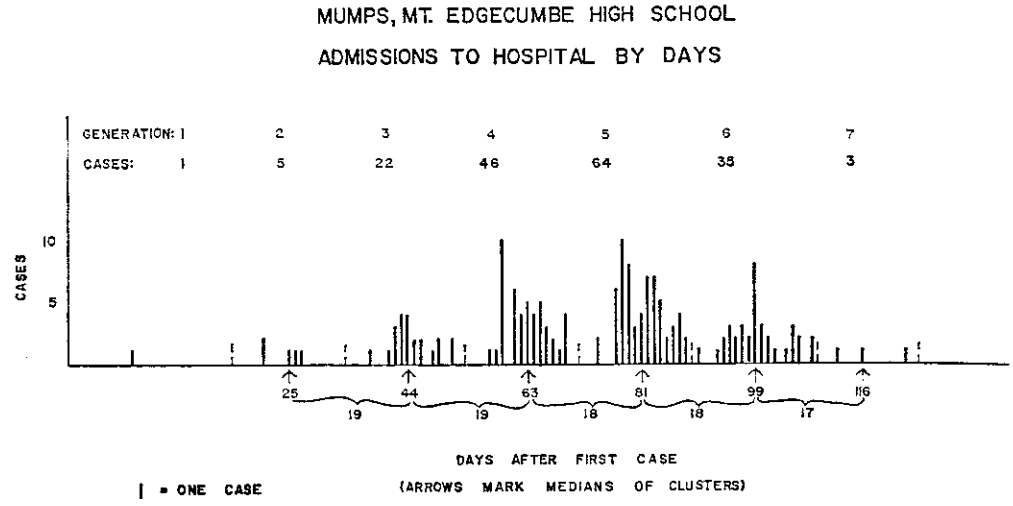

FIGURE 1

tial school on an island near Sitka, Alaska. The course of the epidemic in boys and in girls, who of course lived in separate dormitories, was closely similar, so they are not distinguished in this figure. The dates recorded are of admission to hospital, which usually coincided with the detection of salivary gland swelling. Broken lines separate the clusters of cases believed to represent discrete generations. Generations 2 through 6, and especially 3 and 4, can be quite clearly identified. The median case of each generation is marked with an arrow and the intervals between these medians are given. From the first case to the median of the cluster of 5 considered to represent generation two is 25 days, but it must be recalled that in mumps some 30 per cent of infections are inapparent yet presumably infectious; also that recognition of cases may have been delayed at this early stage. Thereafter, the generations become more reliably determinable as the numbers of cases increase. The most reliably determined intervals are probably those from generation 3 to 4, 4 to 5, and 5 to 6, which are 19, 18 and 18 days, respectively, as measured between medians of clusters. These intervals represent estimates of generation time rather than incubation period; but since in mumps, infectivity begins shortly before onset and extends until shortly after onset (or is curtailed by the child's restricted activity), these two are in fact approximately equal.

The two hypothetical examples furnished in table 6 will help to clarify the statement that the interval between cases in a chain of cases is the generation time rather than the incubation period. Both start from time "0" as the time of receipt of infection by the initial case in the chain of cases being considered. In situation "A", the generation time is 3 days, the incubation period 4 days; in situation "B" the generation time is 5 days, the incubation period again 4 days. The initial case has its onset on day 4 in both instances, but thereafter cases are separated by intervals of 3 days in situation A, 5 days in situation B, despite the fact that incubation periods are equal.

4. Contributing to understanding of pathogenesis. Incubation periods in many diseases, at least as determined in laboratory animals and in some instances in man, vary inversely with the dosage of the infectious agents (15). They are also influenced by the route of administration. Agents which can produce disease when administered either by a "peripheral" and presumably natural route such as throat, lungs or alimentary tract, or by direct inoculation into blood, peritoneal cavity or brain, generally have shorter incubation periods by the latter routes.

The incubation period of rabies is dependent on the distance from the site of inoculation to the head. This fact tends to support other evidence presented by Schindler (16) that the rabies virus travels or is propagated along neural pathways from the location of the bite to the brain. In tetanus also, Tateno (17) has shown that the incubation period is somewhat longer in man after wounds of the extremities than of the trunk and that it is shortest for face and head wounds. This is contrary to what would be expected if the toxin, produced at the site of the wound, were then taken into the blood stream and transported in this way to the central nervous system; it suggests a possible neural or perineural pathway for the toxin, which should be further explored. There are perhaps alternative explanations for the rather small differences in mean incubation period for different wound sites. In any case, the incubation period provides a clue to pathogenetic mechanisms.

Poliomyelitis is another example of this. As previously discussed (6) the interval between tonsillectomy and onset of bulbar or bulbospinal poliomyelitis tends to cluster around the natural incubation period, although tonsillectomy performed at any time in the past is also related to type and frequency of the disease. The interval between inoculation of certain antigens and onset of clinical poliomyelitis is likewise a curve centering, so far as one can tell, about the natural incubation period. This suggests that these precipitating factors operate at the time of initiation of infection, rather than when the infectious process is already under way or several days before infection.

There is some, though rather meager evidence to suggest that in some diseases the clinical severity is inversely related to the incubation period; in other words, the individuals with shortest incubation periods are the ones with most severe illness. Most of the data on this point are from laboratory experiments in which dosage of the infectious agent is varied, and the direct relationship may be between dosage and severity with incubation period being merely an associated variable.

TABLE 6

Intervals in chain of transmission of two hypothetical diseases with the same incubation period but different generation times

	Disease A	Disease B
Generation time in days	3	5
Incubation period in days	4	4
Individuals in chain of transmission	Day of onset (from "0" as day of receipt of infection by case 1)	
1	4	4
2	7	9
3	10	14
4	13	19
.	.	.
.	.	.
.	.	.

The variation of incubation periods in relation to immunity status has not been thoroughly studied. Measles incubation periods are somewhat prolonged after administration of gamma globulin, and this is also true of infectious hepatitis. Since illness is less severe in such partly-immune subjects, the prolongation of incubation periods would be expected from the relationship with severity mentioned in the previous paragraph.

There are, however, situations in which partially immune persons are found to have a shortened incubation period. These are the cases in which hypersensitivity plays a role in the host response to the agent. Vaccinia is a case in point. In primary vaccinia, the vaccinal lesion develops slowly, but in persons who have previously been successfully vaccinated or have had smallpox it develops faster, the speed of development being inversely related to the interval since prior vaccination. One cannot perhaps speak of a true incubation period here, but the pathologic process is under direct observation and the time when the vaccinal lesion begins to develop can be determined.

In an attempt to construct a model to explain the incubation period and the process of infection, several workers have postulated that infection is a stochastic "birth-death" process in which infectious agents are multiplying at a certain rate and being killed off at a lower rate until a threshold is reached, above which symptoms appear. Williams (18) has developed such a model, in which there are 3 parameters. Two of these, the "intrinsic" parameters, are characteristic of the particular disease; they are the initial dosage of infectious units which has an even chance of explosive growth (or ED 50), and the population of infectious units in the host at which symptoms are produced (symptoms threshold). The third, termed the extrinsic parameter, is the actual size of dose, which varies from epidemic to epidemic. Applying his equations to a number of observed epidemics he arrived at predicted distributions of incubation periods which formed smooth curves with slight to moderate positive skewness and which in the majority of the selected epidemics were quite compatible with the observed distributions.

Summary

Following the methods of an earlier study and employing data published by others, the median incubation periods and dispersion factors of some essentially log-normal distributions of incubation periods of diseases are presented (syphilis in rabbits, mumps, chickenpox, smallpox by inoculation, CNS illness after smallpox vaccination, CNS illness after yellow fever vaccination, and tetanus). The influence of size and uniformity of dosage on these parameters in serum hepatitis is illustrated. Four uses for such information are suggested and illustrated. They are: (*a*) judging whether an epidemic is a result of essentially simultaneous exposure of a population to an agent in a common vehicle, protracted exposure to the common vehicle, or propagation from person to person; (*b*) estimation of the time of a common exposure on the part of an affected group; (*c*) determination of the time of maximum infectiousness of a source case; and (*d*) contributing to the understanding of the pathogenesis of disease. The fact that it is the generation time (defined as the interval between receipt of infection and maximal transmission of infection), rather than

the incubation period, which determines the dynamic behavior in propagated infections and the interval between clusters of cases is stressed. The incorporation of information on incubation periods and generation time will be helpful in the development of mathematical models of epidemic phenomena which can be tested against observed epidemics.

References

1. Abbey, H. An examination of the Reed-Frost theory of epidemics. Human Biology, 1952, *24:* 201–233.
2. Maia, J. O. C. Some mathematical developments on the epidemic theory formulated by Reed and Frost. Human Biology, 1952, *24:* 167–200.
3. Bailey, N. T. J. The Mathematical Theory of Epidemics. New York, Hafner Publishing Co., 1957.
4. Brownlee, J. Statistics studies in immunity: the theory of an epidemic. Proc. Roy. Soc. Edinburgh, 1906, *26:* 484–521.
5. Sartwell, P. E. The distribution of incubation periods of infectious disease. Amer. Jour. Hyg., 1950, *51:* 310–318.
6. Sartwell, P. E. The incubation period of poliomyelitis. Amer. Jour. Pub. Health, 1952, *42:* 1403–1408.
7. Mahoney, J. F., van Slyke, C. J., Cutler, J. C., and Blum, H. L. Experimental gonococcic urethritis in human volunteers. Amer. Jour. Syphilis, Gonor. and Ven. Dis., 1946, *30:* 1–39.
8. Oki, Y. Studies on the incubation period of acute infectious diseases from the viewpoint of theoretical epidemiology. Jour. Osaka City Medical Center, 1960, *9:* 2341–2368.
9. Aitchison, J., and Brown, J. A. C. The Lognormal Distribution. Cambridge, Eng., University Press, 1957.
10. Gordon, J. E. and others. Control of communicable diseases in man. 10th edition, New York, Amer. Pub. Health Association, 1965.
11. Hill, B. M. The three-parameter lognormal distribution and Bayesian analysis of a point-source epidemic. Jour. Amer. Statistical Association, 1963, *58:* 72–84.
12. Haygarth, John. A sketch of a plan to exterminate the casual smallpox from Great Britain: And to introduce general inoculation, Vol. II. London, Printed for J. Johnson, St. Paul's Churchyard, 1793.
13. Meyer, M. B. An epidemiologic study of mumps: its spread in schools and families. Amer. Jour. Hyg., 1962, *75:* 259–281.
14. Hope Simpson, R. E. The period of transmission in certain epidemic diseases: an observational method for its discovery. Lancet, 1948, 255 (2): 755–760.
15. Tigertt, W. D., Benenson, A. S., and Gochenour, W. S. Airborne Q fever. Bacteriol. Reviews, 1961, *25:* 285–293.
16. Schindler, R. Studies on the pathogenesis of rabies. Bull. World Health Org., 1961. 25: 119–126.
17. Tateno, Isao. Incubation period and the initial symptoms of tetanus: a clinical assessment of the problem of the passage of tetanus toxin to the central nervous system. Jap. Jour. of Exp. Med., 1963, *33:* 149–158.
18. Williams, T. Stochastic model for incubation periods in infectious diseases. Dissertation submitted to School of Hygiene and Public Health, Johns Hopkins University, 1963, (also see papers in press in J. Roy Statist. Soc. Series B, and Biometrika).
19. Turner, T. B., and Hollander, D. H. Biology of the treponematoses, based on studies carried out at the International Treponematosis Laboratory Center under the auspices of the World Health Organization. World Health Org. Monograph, no. 35, 1957.
20. Stimson, P. M. A manual of the common contagious diseases. Philadelphia, Lea and Febiger, 1947.
21. Conybeare, E. T. Illnesses attributed to smallpox vaccination, 1951–60. Part II—Illness reported as affecting the central nervous system. Monthly Bull. of Min. of Health and Pub. Health Lab. Service, Great Britain, 1964, *23:* 150–159.
22. Fox, J. P., Manso, C., Penna, H. A., and Para, M. Observations on the occurrence of icterus in Brazil following vaccination against yellow fever. Amer. Jour. Hyg., 1942, *36:* 68–116.
23. Spaeth, R. Therapy of tetanus. A study of 276 cases. Arch. Int. Med., 1941, *68:* 1133–1160.
24. Sawyer, W. A., Meyer, K. F., Eaton, M.

D., Bauer, J. H., Putnam, P., and Schwentker, F. F. Jaundice in Army personnel in the Western region of the United States and its relation to vaccination against yellow fever. Amer. Jour. Hyg., 1944, *39:* 337–430.

25. Findlay, G. M., Martin, N. H., and Mitchell, J. B. Hepatitis after yellow fever inoculation. Relation to infective Hepatitis. Lancet, 1944, *2:* 301–307.
26. Spurling, N., Shone, J., and Vaughan, J. The incidence, incubation period and symptomatology of homologous serum jaundice. Brit. Med. Jour., 1946, *2:* 409–413.
27. Allen, J. G., and Sayman, W. A. Serum hepatitis from transfusions of blood. Jour. Amer. Med. Ass'n., 1962, *180:* 1079–1085.
28. Duncan, G. G., Christian, H. A., Stokes, J., Rexer, W. F., Nicholson, J. T., and Edgar, A. An evaluation of immune serum globulin as prophylactic agent against homologous serum hepatitis. Amer. Jour. Med. Sci., 1947, *213:* 53–60.
29. Murphy, W. P., and Workman, W. G. Serum hepatitis from pooled irradiated dried plasma. Jour. Amer. Med. Ass'n, 1953, *152:* 1421–1423.
30. Brightman, I. J., and Korns, R. F. Homologous serum jaundice in recipients of pooled plasma. Jour. Amer. Med. Ass'n., 1947, *135:* 268–272.
31. Unpublished data from U. S. Army records.
32. Hardy, A. V., Frant, S., Jarcho, S. W., and Schlosser, E. G. Studies on the acute diarrheal diseases. IV. An outbreak of bacillary dysentery due to the "Newcastle dysentery bacillus." Pub. Health Rep., 1940, *55:* 2101–2116.
33. Farber, R. E., and Korff, F. A. Foodborne epidemic of group A beta hemolytic streptococcus. Pub. Health Rep., 1958, *73:* 203–209.
34. Commission on acute respiratory diseases. A study of a food-borne epidemic of tonsillitis and pharyngitis due to hemolytic streptococcus, type 5. Bull. Johns Hopkins Hosp., 1945, *77:* 143–210.
35. Mosher, W. E., Wheeler, S. M., Chant, H. L., and Hardy, A. V. Studies of the acute diarrheal diseases. V. An outbreak due to *Salmonella typhi murium*. Pub. Health Rep., 1941, *56:* 2415–2426.