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L. T. Webster

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Research Article

EPIDEMIC PREVALENCE IN THE LIGHT OF EXPERIMENTAL FINDINGS

By L. T. WEBSTER

(From the Laboratories of The Rockefeller Institute for Medical Research, New York)

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This is perhaps a timely occasion to classify and evaluate the results of seven years' experimental study of epidemic diseases. At the annual meetings of this association in 1921, Flexner (1) outlined a plan for the investigation of mouse typhoid infection under the controlled conditions of the laboratory; previously, Topley (2), in London, delivered the Goulstonian lectures on the same subject. Since then, the English investigators, the group at the Rockefeller Institute in New York, and Neufeld and Lange, in Germany, have furthered these studies and brought them to a state suitable for discussion. Hence, although admirable critiques have already been published recently by Neufeld (3), Topley (4), and Flexner (5), it may be of use to summarize briefly our own conclusions, and relate them as far as possible to epidemic prevalence in man.

Furthermore, there is special need at present for a restatement of the general problem, a classification of current theories, and formation of a basis for further investigation. This implies a review of methods and techniques employed, with a discussion of the mutual relationship, advantages, and limitations of each. To these questions, therefore, it is proposed to give attention as well as to summarize briefly the actual results obtained.

The first step in the experimental study of an epidemic disease is the close observation of the infection as it occurs naturally. Knowledge of the distribution of the specific microbes in nature, their portal of entry into the animal body, various types of animal response, etc., is essential. Thus prepared, one is in a position to plan experiments under conditions which are controlled and yet simulate nature, and to attain results which are relatively free of a certain inevitable labora-

tory error, and which may be checked against the observed phenomena of the spontaneous disease.

In this connection, two native diseases have been studied: mouse typhoid, by Lynch and Amoss (6), and later by ourselves (7), and rabbit lepisepticum infection (7). The former is known to be of intestinal origin, the latter respiratory. Both are widespread. Both may persist mildly in a given community, or may assume epidemic proportions with or without apparent periodicity; both prevail more frequently in spring and fall and affect certain individuals and races more severely than others. In short, the two animal diseases present for solution the problems common to human epidemiology.

The second step consists in inducing the various interepidemic and epidemic phases of the diseases in the laboratory under controlled conditions. Both Topley (8) and Amoss (9) have done this successfully with the aertrycke (animal paratyphoid B) mouse typhoid, Topley likewise (10) with mouse pasteurella, and Webster with the *B. enteritidis* mouse typhoid (7) and rabbit lepisepticum infection (7). Topley placed mice in a large cage, introduced the specific bacilli by carriers or contaminated food, and added fresh mice to the population at stated intervals. Amoss placed small numbers of mice in boxes and allowed the attendant to spread the infection from one focus by feeding and cage cleaning manipulations. We have used Topley's method in our mouse typhoid and a modification of Amoss' in our rabbit lepisepticum experiments.

This series of experiments, besides proving that epidemics, resembling closely those occurring "spontaneously," may be induced at will, brought out several other facts of importance. Briefly, they are as follows: (*a*) that a single focus of mouse typhoid in a community is followed by widely scattered sporadic cases (11); (*b*) that the general mortality increases during the pre-epidemic period (12); (*c*) that the addition of fresh individuals into an infected community revives the epidemic (8, 9); (*d*) that the epidemic peak may be maintained by daily replacements of dead with fresh mice (8); (*e*) that survivors may or may not be carriers, or be immune to subsequent infection (13, 9); and (*f*) that the height of the epidemic waves and intervals between them is affected by the rate of immigration of fresh mice,—the greater the immigration rate, the greater is the mortality,

the less pronounced the epidemic wave, and the less apparent the interval between them (10). Thus it was observed that the experimental epidemics reproduce the important phenomena observed in human epidemics and afford an unusual opportunity for analysis.

To explain the mode of spread of the epidemics engendered in the laboratory has, therefore, become the task of the experimental epidemiologist. As his material he has a disease which behaves as human infections do, and which he may use as he sees fit for the solving of the problem. He may regard the phenomena as the result of a mass of indeterminable variables, and hence be forced to apply statistical methods of analysis. He becomes aware that this procedure in no way proves the truth or falsity of any theory, but merely simplifies its statement. In this way he analyzes the data precisely as one would corresponding human data, and goes no further in solving the essential problem. Such an analysis has recently been carried out by Topley (4). On the other hand, he may pursue the experimental method, determine by quantitative measurement the various factors which control the spread of the disease, and determine, as far as may be, their values and mutual relationships. It is this latter method which especially has engaged our attention (14) and hence we shall describe briefly its employment and the results attained.

The three factors responsible for the spread of infection, that is host susceptibility, microbic dosage, and microbic virulence, are, like all biological phenomena, exceedingly difficult to measure accurately. Each is known to be the resultant of a number of variables, of which some are indeterminable. Host susceptibility must be regarded as the sum of the variables which influence the response of the animal to bacteria or other injurious agencies; microbic virulence, the total of the variables which determine their pathogenic power; and microbic dosage, the united variables which decide the number of organisms available to the host. *A priori*, none of the factors can be regarded as a constant and no one may be used uncontrolled as a standard of measurement, as, for instance, host susceptibility and duration of life as measures of bacterial virulence; in short, no uncontrolled response to a given injury may be considered an accurate measurement.

It is essential, therefore, to reduce as far as possible the number of variables contained in each of the three factors. This has been accom-

plished as follows: Dosage has been rigidly controlled by administering to each animal a definite number of organisms by way of the normal portal of entry, thus insuring each animal being exposed in the natural way to a quantitatively known dose. Virulence has been controlled, as far as possible, by keeping bacterial cultures on constant media at 4°C., and using for the inoculation a single culture, freshly grown in a standard fluid medium. Finally, certain variables contained in the host have been eliminated, namely, those due to (*a*) heredity, by using only pure line strains of mice, inbred for five years or more, (*b*) environmental factors, by breeding and raising the mice in a special room, where temperature, food, cage cleaning, space, etc., are standardized. Possible differences, due to (*c*) age and weight, are removed by using young adults ten to twelve weeks old, weighing 18 to 20 grams; and finally, variations resulting from (*d*) acquired, specific resistance are eliminated by keeping the room entirely free from disease. Each mouse, therefore, is known to have had no previous exposure to the organisms. Finally to secure average uniform conditions, 50 to 100 mice are generally employed for each test.

The extent to which control of these factors had been achieved was determined by comparing the mortality rates of different groups of mice inoculated simultaneously with definite numbers of a common strain of mouse typhoid bacilli. If sufficient of the variables had been eliminated, the mortality rates of any number of mouse groups should be the same. And in fact, they proved uniform for each group: the average difference in total mortality among groups of fifty mice was less than 1 per cent per day throughout the sixty day period of observation, of groups of twenty-five, not more than 5 per cent, and of groups of twenty, about 10 per cent (14 and 7). These results show that a significant number of variables had been eliminated from the factors and each factor, under the conditions of the experiment and at a given time, was relatively constant. The mortality curve attained measured quantitatively the reaction between host and microbe and could be considered as a standard. It has been designated, therefore, the "standard control curve" and forms the basis of all our subsequent work (14).

Only with some such standard of measurement is an analysis of

epidemic phenomena made possible, and only by controlling the factors in some such way as we have indicated is one able to obtain such a standard. It is not surprising therefore that Topley, who used mice purchased from dealers, of mixed race, unknown age and environmental circumstances, including previous exposure to infection, has not been able to produce a standard of measurement. His attempts have resulted in widely scattered curves, described by him as totally random. Consequently, his epidemiological experiments contain no satisfactory measurements of the several factors involved and he is driven as in human epidemiological observations to the employment of statistical analyses of the unknown and indeterminable variables. All titration of bacterial virulence must be made against some known standard, where dosage and host factors are known to be constant. The application of this principle is universal throughout the field of bacterial experimentation.

Measurement of the factors concerned in the spread of mouse typhoid and rabbit lepisepticum infection having been carried out in the manner described above, the results attained have been described (14) as follows: Concerning host susceptibility, "we have found that this quality of resistance is present in different amounts in individuals of the same family or race, and that differences, under properly controlled conditions, take the form of a frequency curve. Furthermore, by an artificial selection of especially resistant or susceptible individuals it has been possible to breed strains at will, whose average resistance is greater or less than that of the original random group. It seems probable, then, that successive descendents of two given individuals inherit definite amounts of potential resistance, which vary according to the law of probability about a mean which approximates the mean resistance of the original pair. It would seem that racial differences in resistance to mouse typhoid infection can be expressed by a relatively constant value. And finally, whatever the potential inherited constitution of individuals, families, or races may be, it is affected profoundly by seasonal influences, food, and general hygienic conditions. For this reason it is erroneous to speak of the presence or absence of resistance as though it were a unit factor. Rather it should be considered a manifestation of an extremely complex mechanism,

modified by heredity and environment, whose quantity in individuals of a large group tends to follow the laws of chance, about a mean which is more or less a characteristic of the race" (15).

The virulence of type pure strains of mouse typhoid bacilli and *Bact. lepisepticum* has proved to be constant under conditions comparable to those which occur in nature. There is no geometric rise in virulence before and during an epidemic wave and no corresponding drop at the peak and during its decline. Type pure strains apparently conform to general biological rule and maintain a uniform degree of pathogenicity. It is true that bacterial variation does occur, and that the changed forms are less virulent. Thus, *Bact. lepisepticum* in the presence of oxygen at atmospheric pressure yields variants of low pathogenicity which do not revert to the original form. And mouse typhoid bacilli, in the presence of relatively large amounts of bacteriophage, or other injurious agencies, yield "rough" or "mucoid" colonies, which also are less virulent. But as far as observations of the natural and laboratory diseases have gone there is no indication whatever that these deteriorations play a significant part in the major phenomena of epidemics. The present conclusion, therefore, is that the microbic virulence factor, in so far as the spread of disease is concerned, constitutes a constant.

Microbic dosage, on the contrary, has been found to exert a highly important influence. When the dose is below a certain critical level, the resulting mortality curve is low and irregular; when above, it takes on the characteristic form and is changed but little whether hundreds or thousands or millions of bacilli are available. Furthermore, a critical dose or more of mouse typhoid bacilli given to the Rockefeller Institute strain of mice yields a mortality curve which may be superimposed upon the experimental epidemic curves recorded by Amoss. In keeping with this the demonstration has been made experimentally that in course of mouse typhoid epidemics the number of bacilli available to a given population increases from a negligible quantity to several millions six to eight days before the onset of an epidemic wave, and drops below the critical point a few days preceding the decline in mortality (14).

The bearing of these various observations and measurements on the theory of epidemic prevalence is considerable. Among other

things it becomes necessary to substitute for "change in virulence" the notion of "change in host susceptibility and dosage." The experimental data provide support for certain observations on differences in individual resistance which clinicians have long held as self-evident, and suggest an explanation as to the manner of spread of diseases such as exanthemata, influenza, and pneumonias, less well understood than those we have described.

Three hypothetical states of equilibrium of any population in respect to a given microbe may be recognized; the community may be entirely free, it may harbor the more saprophytic forms of low virulence, or it may contain scattered foci of the virulent forms. In the first instance, an epidemic arises by a widespread distribution of virulent organisms coming from without, in the second, possibly by a widespread dissociation or mutation and distribution of already present, non-virulent types to virulent forms, and in the third, by dissemination of already present virulent forms throughout the population. In typhoid-dysentery outbreaks, due to food or water contamination, in influenza epidemics, primary plague, cholera, and syphilis epidemics such as prevailed in western Europe during the thirteenth, fourteenth, and fifteenth centuries, the virulent microörganisms were certainly introduced from without. Whereas in the urban typhoid-dysentery out-breaks which still sometimes arise, in present-day pneumonias, exanthemata, common colds, oriental plague, and cholera, the inciting virulent microörganisms are undoubtedly already present in the given community. There is no present evidence indicating that saprophytic microörganisms of low virulence present in a community undergo an increase in pathogenicity or mutate, become widespread and excite epidemics. Virulent or so-called "epidemic" strains of microörganisms must, therefore, either be introduced into a community from without, or be already present in scattered foci.

The mechanism underlying microbic distribution has still to be explained. Probably population susceptibility plays a large part. Extraneous microbes introduced into a virgin population find a large proportion of susceptibles. In them, they multiply rapidly and thus become widespread. Microbes already present in a community must likewise increase in numbers in the tissues of susceptibles. Measles becomes epidemic every second or third year in New York,

as the number of susceptibles increases above the critical level; pneumonia increases in the spring and fall at the time when deaths from all causes increase and susceptibility seems greatest; oriental plague and cholera, war-time epidemics occurring at periods of stress and strain on population resistance, all suggest some relationship between altered resistance and increase in dosage.

However this may be there is no doubt that adequate available dosage is the essential incitant of an epidemic, and experiment has shown that the actual curve, morbidity or mortality rate, is an expression of the resistance, hereditary and acquired, specific and non-specific, of the population group exposed to a given dose of pathogenic microbes. When microbic distribution has been sudden and widespread throughout a susceptible population, a simple left skew frequency curve results; when dosage is intermittent, plateaus and multiple peaks occur, and when population resistance is high, the curve becomes gradual and low. Morbidity or mortality rates describe actual host susceptibility to a given dose of microbes and not fanciful fluctuations in microbic virulence.

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