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Experimental Epidemiology: DR. LESLIE T. WEBSTER 445

Obituary:

Louis Agricola Bauer (1865–1932): J. A. F. *Wilhelm Ostwald:* PROFESSOR WILDER D. BANCROFT. *Recent Deaths* 452

Scientific Events:

The International Congress of Mathematicians; Zoological Sessions at the Summer Meeting of the Association; Award of the Osborne Medal to Dr. C. H. Bailey; The American Philosophical Society 455

Scientific Notes and News 457

Discussion:

The Field Naturalist in the Final Interpretations of Life: H. A. ALLARD. *Spontaneous Combustion in the Marshes of Southern Louisiana:* PERCY VIOSCA, JR. *Rhythmic Phenomena in Gels:* J. M. JOHLIN. *Behaviorism in Science:* PROFESSOR WILLIAM D. TAIT 460

Quotations:

International Cooperation 463

Scientific Apparatus and Laboratory Methods:

Influence of Method of Shaking on Amount of Phosphate Dissolved from Soil by Water: PROFESSOR P. L. HIBBARD. *A Method of Artificially Feeding the Sugar-beet Leafhopper:* J. M. FIFE 464

Special Articles:

Visual Purple in Snakes: DR. GORDON L. WALLS. *A Note on the Flow of Fluids through Porous Media:* DR. GEORGE H. FANCHER and JAMES A. LEWIS 467

Science News 10

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EXPERIMENTAL EPIDEMIOLOGY[1]

By Dr. LESLIE T. WEBSTER

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EPIDEMIOLOGY, according to common usage, is knowledge of the mode of spread of infectious diseases. This knowledge is especially concerned with epidemics and endemics, long-time and short-time cycles of disease prevalence, general and local extension of disease and relative severity of disease in racial and familial groups and in individuals. Data, mostly descriptive and poorly organized, accumulating for centuries, were simplified in part by experimental pathologists and bacteriologists at the close of the nineteenth century into several principles, a postulate and a theory.

Considered chronologically, the first two principles are the communicability of certain diseases and the living specific nature of their known incitants. This knowledge was present in substance 4,000 years ago in popular superstitions and beliefs but was not established on an experimental basis until Bassi transmitted silkworm muscardine in 1835, Remak transmitted favus in 1840, and Brauell, Pasteur, and Koch transmitted anthrax in 1857 to 1890. Three additional principles, namely, the operation of host resistance, diet and climatic factors influencing the spread of infectious disease, were likewise recognized from earliest times, but are only recently being studied experimentally. The last two, the doctrines of the carrier state and of specific immunity, established by Koch and by Behring and Kitasato, respectively, are modern both in concept and experimental proof.

Knowledge of infection underwent further organization during the Pasteur-Koch period. Theurgical and supernatural doctrines of epidemics were dis-

[1] Cutter Lecture on Preventive Medicine, 1932. Harvard University.

carded, and the possible effects of cosmic, constitutional and subsoil influences came to be ignored. In their places a postulate was made by students of descriptive epidemiology, that all phenomena of infection can be accounted for in terms of three factors—virulence of the specific agent, dosage of the agent available to the host and resistance of the host to the specific agent. This postulate has since been accepted by the majority of epidemiologists.

Strangely enough, however, except for the studies of Theobald Smith and of plant pathologists, few efforts have been made to test the postulate experimentally, or to analyze the mode of operation of the hypothecated microbic and host factors. The descriptive epidemiologist is working with vital statistics which contain uncontrolled sources of error, the bacteriologist is studying the problem of microbic virulence in artificial infections and in artificial media, without determining whether his findings are in any way related to the behavior of microorganisms in their native host, and the immunologist is gaining knowledge of the specific substances found in the blood of individuals who have been exposed to an antigen, but is slow to investigate the extent to which these specific substances are related to the resistance of the host under natural conditions.

The postulate of the rôle of parasite-host factors was, in spite of the lack of experimental testing, further simplified by bacteriologists and immunologists into a theory that the spread of infectious disease is determined in the main by fluctuations in virulence of the specific agent and fluctuations in the specific acquired immunity of the host. This prevailing view has of late, however, been subjected to much criticism. Some investigators urge that bacteriology alone does not explain all the mass phenomena of epidemics and consequently that unknown forces should be given further consideration. Others believe that more attention should be paid to the demonstrable phenomena of host, climate and dietary influences. Increasing numbers regard epidemiology as not reducible to bacteriology and immunology alone, and demand a type of investigation which deals with conditions more closely similar to those in nature.

To meet this need, a new field of research has been developed. Shortly after the influenza pandemic of 1918–1919, investigations were commenced by Topley in London and by Flexner and Amoss in New York, to determine experimentally the general mechanisms underlying the spread of infectious disease. These studies, continued and amplified by others in the past eleven years, have come to be regarded as a definite discipline—experimental epidemiology.

This discipline is far-reaching in scope. It affords a means of acquiring relevant and at the same time controlled data on the spread of one or a number of animal infections. It affords a hope that this sort of information of a number of infections in a number of species of native hosts may be simplified into a theory which will describe a part of the epidemiology of animal and of human infections as well.

The technique of experimental epidemiology has been to study the mode of spread of native infections among populations of laboratory animals. Thus far a total of nine enteric and respiratory infections of rodents and fowls has been analyzed by observations both on population infections occurring spontaneously, and induced experimentally, and by measurements of virulence, dosage and host resistance, especially during the actual spread of infection. The technique has been put to use in two different ways. Topley and Greenwood experiment with *aertrycke* infection of mice chiefly to throw light directly on the perplexing questions of human epidemiology; we, on the other hand, study the spread of an animal infection as an end in itself and extend the study to different native infections in different host species with a view to building up an experimental science. The details of the technique have differed according to the emphasis placed upon control of variables and adherence to natural conditions. Some investigators have made relatively few efforts in their experiments to control host variables and in many instances to reproduce natural conditions. Their efforts have rather taken the direction of attempting to interpret data by subjecting them to the ordinary analyses used in the study of vital statistics.

It is to be assumed, however, that since one or many factors may conceivably influence the spread of infection, the greatest possible control of all is to be desired. Therefore, in recent experiments at the Rockefeller Institute every effort has been made to control not only the microbic but especially the host variables. The animals employed are born and raised in special breeding rooms on the premises. Their heredity, age and weight are known; their allotted space, cleaning routine, food, temperature and light are kept uniform. The animals are known to have been free of any previous exposure to the given infection. Finally, when microbic virulence, dosage and host resistance factors are being analyzed, it is to be assumed that a technique reproducing natural conditions in the greatest degree is most apt to yield results which are applicable to the phenomena of natural infection. Hence, in the institute laboratories the specific bacteria are introduced into the native hosts not by intraperitoneal injection but by way of the normal portal of entry. These procedures

give results which reproduce events in nature and which at the same time are quantitative.

Early experiments showed that natural infection could be established in susceptible populations by administering pure cultures of specific bacteria to constituents or immigrants. Amoss, in 1922, fed mouse typhoid cultures to ten mice and placed them in two cages in the midst of 100 normal mice in twenty cages. Shortly thereafter, the specific infection was fatal to eight of the original mice and spread to the normal animals. Later, four batches of mice were added and the infection extended to each group in turn. Recently Friedländer pneumonia was established in four populations of mice in our laboratory by administering 500 bacilli intranasally to certain constituents—in one experiment the entire group received the organisms and normal immigrants were added thereafter at the rate of two per day for three and a half years; in two further experiments three groups of 100 mice each received six immigrant mice which had been given 500 Friedländer bacilli intranasally. Healthy immigrants were added thereafter for two and a half years and eight months, respectively. In each case the Friedländer infection spread from the immigrants to the healthy population and became established with endemic and epidemic phases identical with those of the spontaneous disease.

Early experiments likewise showed that epidemics could be induced in populations under two definite sets of conditions. First, in previously unexposed communities, by administering to each individual a certain dose of the specific organisms by way of the natural portal of entry, and second, in already infected populations, by adding susceptible immigrants. Epidemics of mouse typhoid were incited in previously unexposed populations by administering three to five million bacilli in broth intrastomachally to batches of 20 to 100 mice. The resulting mortality over a sixty-day period in averaged tests was characteristic and practically identical with that occurring during spontaneous epidemics. Epidemics of Friedländer pneumonia were incited in previously unexposed populations by administering 500 bacilli in broth intranasally to batches of 50 to 100 mice. The resulting mortality over a thirty-day period was uniform in averaged tests and similar to that occurring during spontaneous epidemics. In infected populations, outbreaks of mouse typhoid were incited by adding batches of normal susceptible immigrants. Following some suggestive observations of Topley in 1919, Amoss assembled 100 healthy mice in twenty cages of five mice each and midway placed two additional cages of five mice each, which had been fed on a culture of mouse typhoid bacilli. Four weeks later forty additional cages, containing five mice each, were placed near the first batch. Subsequently, sporadic infection occurred, fatal in three months to about 50 per cent. of the population. The survivors were recruited to their original numbers by replacements in each cage to five mice. Within a few days an epidemic of mouse typhoid occurred, fatal to 70 per cent. of the herd in two months. A second and third replacement was made, followed by outbreaks of decreasing severity. These results were confirmed in 1925 by Greenwood and Topley, who showed that the repeated addition of normal individuals to mouse populations infected with Pasteurella is followed by recurring epidemic waves. Likewise, experiments at the Rockefeller Institute in 1930 showed that if immigrants were added to one of three mouse populations infected with *B. friedländeri,* recurrent epidemics of pneumonia ensued, while if at the same time and under identical conditions, immigrations were discontinued in two remaining populations, no epidemics occurred and the infection died out.

Topley and Greenwood, in further observations on infected mouse populations, emphasized the close association between the amount of mortality and the number of susceptible immigrants. They found that when mice were added to an infected herd at a constant rate, the mortality was propagated in regularly recurring waves and suggested that the character of the waves was dependent upon the rate of addition of immigrants. We observed later that when four or more populations of mice infected with *B. friedländeri* were recruited at the rate of two mice per day, the primary epidemic waves of pneumonia occurred when the population had reached a certain level, lasted a definite number of days, and reduced the population census to a definite low level. Moreover, when *B. enteritidis* typhoid was spreading under identical conditions in uncomplicated form in these communities, the mortality waves occurred with considerable regularity at nine to eleven day intervals. It is concluded, therefore, that epidemics may be incited in already infected herds by the proper addition of susceptible immigrants, and in unexposed populations by administering to each individual a certain dose of the specific organisms.

Early in these studies, Topley observed that, following epidemics of mouse typhoid there are a certain number of survivors and stated that these survivors are both potentially infective and relatively immune. Evidence of the immunity of survivors was obtained later in our laboratory by actually comparing the resistance of surviving and non-exposed mice. Mouse typhoid organisms were administered by mouth to 100 individuals; sixty days later there were thirty-two survivors. These together with twenty normal,

unexposed mice, were then given a similar dose of bacteria. Sixty days later, 30 per cent. of the survivor group had succumbed, as compared to 80 per cent. of the control group, showing that by actual test survivors are more resistant than non-exposed animals to the given infection.

The results thus far described demonstrate that various endemic and epidemic phenomena of natural enteric and respiratory infections may be reproduced experimentally solely by the proper bringing together of susceptible hosts and pathogenic microorganisms, thus furnishing experimental evidence for the postulate brought forward by followers of the Pasteur-Koch school fifty years ago. The second accomplishment of these experiments has been to afford an opportunity for analyzing the microbic and host factors under natural and yet controlled conditions, that is, to determine whether virulence does vary during epidemics and whether epidemics are brought to an end by the population acquiring a specific immunity.

Attention will be first given to the virulence factor. That the virulence of a microorganism, that is, its capacity to harm its native host, is a highly labile variable is an assumption founded upon the early observations of Davaine and Pasteur. This idea, supported later by bacteriologists, has come to form the basis of modern epidemic theory. The experimental epidemiologist, however, recognizing that the data are derived from tests which are now regarded as inadequate, has interested himself in the potency of bacteria under conditions as nearly natural as possible.

One series of tests showed that typical strains of organisms from infected animals were of uniform virulence, whether recovered early or late in the course of disease. For example, each of two cultures of mouse typhoid organisms were given intrastomachally to twenty mice, one from the heart's blood of an animal dying five days after exposure to mouse typhoid; the other from the tail vein of a mouse with septicemia, surviving the infection for five weeks. The acute septicemic culture proved fatal to fourteen; the chronic septicemic culture to twelve mice.

Other tests showed that strains of mouse typhoid, Friedländer and fowl cholera organisms from healthy carriers were in general of the same virulence as strains recovered from fatal cases. Thus, each of three strains of *aertrycke* mouse typhoid organisms was given by mouth to twenty mice, one a culture from an acute septicemic case, two others from stools of two mice surviving and healthy five weeks after exposure. The mortalities were 70, 70 and 65 per cent., respectively. Tests with *B. enteritidis* mouse typhoid gave similar results. Several strains of mouse Friedländer organisms were administered intranasally to batches of fifty or 100 mice in comparable doses. In one instance, a lung culture from a fatal case was compared with a culture obtained from a healthy carrier. Each was given to 100 mice intranasally. The resulting mortalities were 70 and 65 per cent., respectively. Tests were made with thirty fowl cholera strains from fatal cases and forty strains from healthy carrier fowl on several commercial farms. Each strain was administered into the nasal cleft of twenty specially bred young birds. In general, strains from fatal cases proved to be of the same virulence as similar strains from healthy carriers.

Further experiments indicated that strains of specific organisms recovered from populations at various endemic and epidemic periods of spontaneous infection were of uniform virulence. Epidemics of fowl cholera and rabbit-snuffles pneumonia, mouse typhoid and mouse pneumonia were studied in our laboratory, epidemics of guinea-pig and rabbit Pasteurella and pneumococcus pneumonia by Neufeld in Berlin, and epidemics of guinea-pig typhoid by Theobald Smith at Princeton. In no instance were significant differences in the virulence of pre-epidemic, epidemic and post-epidemic strains detected.

Still other tests showed that strains of the same organisms from different populations may differ in virulence and in general that the strains with high potency for killing the native host possessed relatively little ability to vegetate in the tissues of survivors and *vice versa*. This latter relationship is illustrated by experiments in which an epidemic or endemic strain of fowl cholera organisms was administered intranasally to young chickens and permitted to spread to healthy contacts. The tendency of the epidemic strain to kill but not to spread, in contrast to the tendency of the endemic strain to spread but not to kill, was consistent. The same differences were demonstrable with epidemic and endemic strains of rabbit Pasteurella.

One further series of tests may be mentioned briefly—namely, those of the effect of animal passage on virulence. Since the early days of bacteriology, cultures have been transferred from animal to animal for the purpose of enhancing their virulence. The tests have been made for the most part in some foreign animal host and by means of some artificial method, such as intraperitoneal injection, and the results, although definite in a few instances, have usually proved equivocal. Nevertheless, they have been employed to support the idea that prior to an epidemic the virulence of the specific agent increases by means of passage from host to host. The present tests were made under conditions as nearly natural as possible. Mouse typhoid organisms from heart's

blood or intestinal contents of animals in the acute stages of infection were given intrastomachally to batches of mice without intermediate cultivation on artificial media. Such passages were made serially and repeatedly. Similar tests were made with Pasteurella cultures native to rabbits, and fowl cholera organisms native to chickens. In no instance was a significant increase in virulence demonstrable.

In summary, the effective virulence of a given strain of microorganisms, when analyzed under natural and controlled conditions, has proved to be a relatively stable property and to some extent inversely related to its ability to survive in the tissues of its natural host. The virulence of numbers of strains of the same organism in the same community was uniform, while the virulence of strains from different communities was at times dissimilar.

The second epidemic factor to be analyzed was microbic dosage—the number of organisms available to the individual host or to the total population at a given time. The findings may be summarized as follows. Changes in dosage exerted a direct effect upon mortality, when virulence and resistance were constant. As dosage was increased, there ensued a progressive increase in percentage mortality up to a point less than 100 per cent. Thus, in a titration of mouse Friedländer bacilli, each of eight doses of the organisms given intranasally to twenty-five mice resulted in mortalities of 32, 44, 56, 64, 88, 96 and 96 per cent., respectively. The second finding has been referred to before, namely, that by giving mice proper doses of typhoid or Friedländer organisms, it is possible to reproduce closely the events of explosive, spontaneous epidemics. Finally, it will be pointed out in tests referred to later that during the actual spread of infection in populations, dosage increased prior to epidemics and decreased prior to their decline by a time interval which approximated that of the incubation period of the infection.

Host resistance, the third epidemic factor, was found to be made up of both non-specific and specific components. The non-specific component was present in definite amounts in breeds or races of animals. For example, monthly tests of the resistance of an inbred strain of mice to mouse typhoid organisms were made from 1922 to 1926. The results in terms of mortality were averaged each year and found to approximate each other within 2 or 3 per cent. Similar tests with other enteric and with respiratory infections and tests with other strains of mice gave similar results. The non-specific components of resistance were present in different amounts in different races or breeds. Thus, a black Lathrop strain, pen inbred for twelve generations, proved on nineteen consecutive monthly tests with *B. aertrycke* and several consecutive tests with *B. enteritidis* mouse typhoid to be more susceptible than the Rockefeller Institute mice. Albino Swiss strain mice, also highly inbred, and albino Rockefeller Institute mice were raised on four different diets. In each case the Swiss mice proved more susceptible. Repeated tests with white-faced and black and tan strains, brother and sister inbred, showed them to be more susceptible than the Rockefeller Institute line.

The non-specific component of resistance was also proved to be present in different amounts in individuals of the same breed. Thus, whenever a controlled group of animals is given a definite dose of some harmful agent, such as $HgCl_2$, individuals show markedly different types of response, ranging from death after the briefest interval to a complete refractory state. Again, whenever a group of animals without previous exposure was given a native infection by the normal portal of entry, individuals showed markedly different types of response, ranging from death after the briefest incubation period to a complete refractory state. These differences were the more regular and predictable when every precaution had been taken to insure uniformity of inheritance, environmental conditions and food. In *B. aertrycke* mouse typhoid, for example, when groups of mice were given bacilli intrastomachally, 70 per cent. died with positive blood cultures in a period of five to sixty days, while 30 per cent. survived. Of these latter, about 10 per cent. were recovered cases, with positive agglutinins, while 20 per cent. showed no evidence of infection. Again, when rabbits were given a similar dose of Pasteurella intranasally, 28 per cent. died of pneumonia, of acute interstitial, lobar, or chronic empyema types, 44 per cent. showed merely local rhinitis or sinusitis, 13 per cent. became healthy carriers, and 14 per cent. remained uninfected. Similar quantitative effects followed the administration of fowl cholera organisms to chickens. These findings have been confirmed by workers in Neufeld's laboratory in their studies of Friedländer and pneumococcus infections of mice. In short, individuals submitted to precisely the same risk of infection, under identical conditions, where every known factor was controlled, exhibited profound differences in response.

That these differences in the reaction of individuals are due to amounts of non-specific resistance which are inherited was shown by the results of tests on survivors and by breeding experiments. Thus, mice surviving an intrastomachal instillation of mouse typhoid organisms proved more resistant to an instillation of mercury bichloride than normal mice. Most significant, however, is the fact that the progeny of mice surviving *aertrycke* or *enteritidis* typhoid were

more resistant to subsequent infection with mouse typhoid bacilli or to doses of mercury bichloride than normal, unselected mice; and conversely, progeny of mice, succumbing early to typhoid, were more susceptible than unselected mice. A further study of the inheritance of different degrees of susceptibility is now in progress. Five hundred female and one hundred male mice of the Rockefeller Institute strain were mated, one male to five females. When the young were weaned, the six hundred parents were given intrastomachally three million *enteritidis* mouse typhoid bacilli. In cases in which both parents died within ten days after infection and in which, on the other hand, both parents survived sixty days, the respective litters from susceptible and resistant parents were saved for further breeding. Simultaneous tests of resistance have since been made on progeny of six generations of the original susceptible and resistant group together with an unselected control group. The possibility of specific immunity developing from infected animals was definitely ruled out by repeated carrier and autopsy tests, by testing the population for carriers, by testing animals found dead for mouse typhoid organisms, and by housing the progeny of susceptible and resistant lines together in the same cage for four weeks. The stock has remained free of all infection. Thus far, five lines of susceptible mice and six lines of resistant mice have been selected. The susceptible lines show approximately 95 per cent. mortality within fifteen days after exposure; the control group shows 35 to 40 per cent., and the resistant lines show approximately 5 per cent. mortality over the sixty-day period of observation. The same relationship holds when the resistant mice are given ten times the dose and the susceptible mice 1/100 of the standard dose. The final and necessary test of the resistance of these mice was their response to exposure to spontaneous infection. Cages were arranged to contain five unselected mice given five million *B. enteritidis* per os, together with five normal mice from the susceptible lines and five from the resistant lines. In each instance, all or nearly all the contact susceptible mice contracted the infection and died, while all or nearly all the resistant mice survived and remained healthy. These results prove that of five hundred individuals selected at random, some possess a greater and some a less amount of resistance to *B. enteritidis,* which is transmitted quantitatively to their progeny.

Non-specific components of resistance, besides being inherited, are affected by environmental factors such as season and diet. Thus, each month over a period of years, batches of 50 to 100 mice have been given mouse typhoid or Friedländer organisms with the result that mortalities, although irregular, have been definitely greater during the winter than the summer seasons. Again, mice raised on various adequate diets differed markedly in resistance. One diet containing bread and milk has sufficed to raise the Rockefeller Institute stock and about one thousand progeny per month for more than fifteen years. The fertility, duration of life, weight, appearance and general health of these animals are excellent and have become standard. Another diet used by McCollum has proved adequate for his rodent stock, and a third, a modified Steenbock ration, has likewise proved satisfactory. And yet, mice raised on the bread and milk diet are far more susceptible to *enteritidis* and *aertrycke* mouse typhoid, botulinus toxin and mercury bichloride poisoning than mice fed on McCollum or Steenbock formulae. No intensive efforts have been made thus far to analyze these differences beyond demonstrating that butter fat and cod-liver oil added to the bread and milk changed the "susceptible" into a relatively "resistant" diet. Environmental factors, other than those tested, such as exercise, fatigue and exposure, probably exert some influence on the resistance mechanism of the host, but as yet have not been submitted to adequate tests.

The known specific components of resistance appear to be acquired as a result of contact with the specific agent. Just how potent these specific components may be and how important epidemiologically they may prove has not been determined. Perhaps the most complete test of these questions has been reported by Topley and Greenwood. Animals were vaccinated with killed cultures of *B. aertrycke* and exposed to infection by being placed in an infected population. The amount of protection conferred was claimed to be significant only when a certain type of flagellar vaccine was employed, and then only when the exposure was mild and of brief duration. The protection was not a permanent one; it was noted during periods of about ten to thirty days after exposure.

Thus far, the analyses of host resistance to infection have shown that individual animals exhibit definite amounts of non-specific inherited resistance to primary infection which take the form of a frequency distribution characteristic of the breed or race. Moreover, this resistance may be added to or detracted from by environmental influences, such as season and diet, and may be supplemented by specific immunity components acquired as a result of contact with the specific microbic agent.

The effect of the resistance factor on the spread of infection proved to be important. In the first place, when individuals of a group were given the same dose of organisms of a certain virulence, they died at varying intervals depending upon individual dif-

ferences in non-specific resistance. Moreover, when a similar group suffered a spontaneous epidemic under controlled conditions, they died at intervals similar to those in the experimental group, indicating that in both instances the form of the epidemic curve was probably controlled largely by the same factors, namely, differences in individual resistance to a large dose of organisms of stable virulence. In the second place, it became apparent that the prevalence of these infections in controlled communities was determined to a great extent by variations in population resistance.

The rôle of resistance and of virulence and dosage as well in actually inciting epidemics was studied in rabbit and fowl populations infected with Pasteurella and in mouse populations infected with Friedländer and *enteritidis* organisms. As the events in all communities were similar, the present description will be confined to those occurring in the mouse herds.

Mice constituting each population were assembled in single large cages and maintained on the routine diet of bread and milk. To each population two normal mice with identification marks were added daily. A census was kept each day and the animals found dead were removed, autopsied and cultured for the presence of the specific organism.

The first experiment was made to test the mode of spread of Pasteurella in communities previously unexposed to these organisms. Populations 1, 3 and 4 received rabbit strains; Population 2 a fowl strain. The three rabbit strains infected few of the mice and died out at once; the fowl strain behaved in quite a different manner. Eight of the ten mice originally fed died within two weeks with Pasteurella septicemia, after which no further deaths from this infection occurred for six weeks. At that time, however, one of the immigrants succumbed. Three weeks later, when the population numbered 61 individuals, explosive epidemics of Pasteurella arose, fatal to 77 per cent. of the population in five days. The epidemic then ceased abruptly and Pasteurella disappeared from the community. The virulence of strains obtained during the epidemic proved to be uniform and similar to that of the culture originally introduced into the community.

The next experiments dealt with explosive and highly fatal epidemics of Friedländer pneumonia which appeared spontaneously in the mouse populations. In the communities to which daily immigrations of two mice were discontinued, the infection died out; in the communities to which daily additions were continued, characteristic secondary waves ensued. These waves appeared when the population census reached a certain level. They lasted a relatively similar number of days and reduced the population to a similar low census. Subsequently, endemic periods intervened, followed by the disappearance of the disease in the late winter. During the next summer, epidemics broke out again similar in each population but more protracted than the previous ones. Fewer secondary waves ensued and the disease disappeared sooner. The virulence of the Friedländer organisms, as determined by their ability to spread and incite typical epidemics, in herds of previously unexposed mice, and by direct inoculation titrations during pre-epidemic, epidemic, post-epidemic and inter-epidemic phases of the infection, proved to be constant. The carrier rate increased prior to epidemic outbreaks and decreased shortly before the time of peak mortality. A substitution of relatively susceptible for standard immigrants in a given population was followed by an increase in severity and frequency of epidemics, while a reverse substitution of resistant for susceptible immigrants was followed by a fall in the severity of the infection.

The final experiments were made with *enteritidis* mouse typhoid in the same mouse populations. The infection took the form of periods of low-grade mortality, interspersed with epidemiform outbreaks. The daily deaths in the one case were either relatively constant or rhythmic in nine-day intervals; the sudden increases in mortality were invariably associated with some definite environmental disturbance. Cultures of the organisms taken from healthy carriers or mice dead of typhoid during pre-epidemic, epidemic or inter-epidemic phases of infection were of uniform pathogenicity. Furthermore, the bacterial dissociation and bacteriophage phenomena, although abundantly present, seemed to play no part in determining the spread of infection. The dosage of the organisms available to the population increased just prior to an increase in death rate and decreased in like manner before a fall in death rate. Most important were the experiments made to test the effect of changing population resistance on the prevalence of infection. Increasing population resistance by substituting an optimum for a barely adequate diet or by substituting relatively resistant for susceptible immigrants each day inaugurated periods of relatively low death rate; on the contrary, a depression of population resistance by substituting the barely adequate for the optimum diet, or the susceptible for the resistant immigrants was followed by severe epidemic outbreaks.

This concludes the present findings in experimental epidemiology. It has been noted that various phenomena of population infection can be reproduced experimentally by the proper bringing together of host and microbic factors. In these native infec-

tions, spontaneous or experimentally induced, the virulence of strains of microorganisms from different populations was occasionally different—the more virulent being the less vegetative—but the effective virulence of strains in any one community proved stable during the entire endemic and epidemic periods of observation. The dosage and host resistance factors, on the contrary, varied significantly with the amount and severity of infection. Expressing these relationships in terms of cause and effect, it appears that infections in these animal populations were controlled by stable virulence and varying dosage and resistance factors. In instances in which a foreign microorganism gained access to a hitherto unexposed population, the inherent virulence, the available dosage and the amount and distribution of non-specific population resistance together determined the extent and severity of the infection. In instances in which a microorganism was already present in the population, variations in population resistance and in available dosage were chiefly responsible for endemic and epidemic prevalences. Fluctuations in population resistance were brought about by immigration, season and diet acting upon the non-specific components, and by the infecting agent stimulating the specific components of resistance. Fluctuations in available dosage resulted from variations in the host resistance and vector factors.

To what extent is this knowledge obtained by experiment consistent with the known facts of human epidemiology? Briefly, there is evidence that the factors related to microbe and host suffice to account for the usual manifestations of cholera, typhoid and the insect and animal-borne infections; there are no data indicating that these factors may not likewise suffice in other human infections. Concerning the operation of these factors, there are grounds supporting the view that infections transmitted by vectors or contracted from foreign hosts, and infections transmitted by water, milk or food are for the most part controlled by a fluctuating dosage factor operating on a population of fluctuating resistance. These diseases, taken together and considered from the tempero-geographical view-point, constitute the great majority of the total number. Added to them are the parasitic and skin infections, whose prevalence appears likewise to be controlled by the host and dosage factors. The remaining group of respiratory diseases transmitted by direct contact, relatively very small but common to this climate, and therefore of great interest, are at present not as well understood. One can but state that the available data do not discredit the view that their prevalence too is controlled by fluctuations in dosage of and resistance to specific agents of relatively fixed virulence.

Further knowledge of the spread of human infections is being obtained by methods similar to those of experimental epidemiology. Opie's studies on the spread of tuberculosis in families, Paul's observations of families with rheumatic disease, the work on the spread of upper respiratory tract pathogens among small groups of individuals, and detailed bacteriological, clinical and sociological investigations of circumscribed communities throw light on the manner and extent of dissemination of the specific agents and the relation of variations in dissemination, that is, in dosage, to variations in amount and severity of the infection in these communities. They give promise to make more clear the rôle of resistance and whether it consists primarily of inherited non-specific factors on the one hand, or of acquired specific factors.

To broaden the scope of experimental epidemiology the studies must be extended from the acute, highly fatal, bacterial diseases of animals to the more chronic ones and to virus infections. This last step is already being taken. Knowledge of many types of infection in many species of hosts will be required for the proper development of epidemiology as a science.

OBITUARY

LOUIS AGRICOLA BAUER (1865–1932)

THE death in Washington on April 12, 1932, of Louis Agricola Bauer, the original director and, since 1930, director emeritus of the Department of Terrestrial Magnetism of the Carnegie Institution of Washington, removes from science an internationally recognized authority in the field of his especial interest. Almost solely on account of his enthusiasm and organizing ability, the systematic magnetic survey of the whole earth both on land and on the oceans has been accomplished within the past twenty-five years, by which an empirical basis has been established for theoretical discussions of the origin and behavior of the earth's magnetic field which would otherwise have long remained impossible. While the recognition accorded Dr. Bauer rests largely on this monumental achievement in accumulating a vast amount of observational information, he has also been among the foremost in the discussion of not only terrestrial magnetism but of other related geophysical problems, as is evidenced by the long list of titles with which he is accredited.

Born of German-American parentage on January 26, 1865, in Cincinnati, Ohio, Dr. Bauer received there his early training and obtained from the University of Cincinnati the degrees of civil engineer (1888) and