THE IMMUNOLOGIST AND THE EVIL SPIRITS[1]

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One of the Association's few requirements of the president is acceptance of the honor of addressing its members at the annual meeting. Selection of the topic of discussion, which is left to the discretion of the speaker, is difficult because of the varied interests of the group. Moreover, the choice of topics appears to be limited because it is the consensus of most interested persons that infections, for all practical purposes, have been eliminated. It is conceded, perhaps, that a few things of academic interest remain to be done, such as synthesis, by the chemists, of antibodies, and ferreting-out, by combined activities of chemists and mycologists, of Ehrlich's "therapia sterilisans magna." But it is generally assumed that the chief problems have been solved. Those obvious conclusions, however, are orderly deductions by well informed minds. The honor of addressing the Association this year falls to one with a simple mind. Such minds belong, perhaps, to the uneducable; and an apparent quality of uneducability is temerity. And, it is temerity that enables one to question obvious conclusions, and to use, with neither blush nor apology, the title "The Immunologist and the Evil Spirits."

We rejoice in our complete emancipation from the concept of evil spirits; we boast, proudly, of our knowledge of infectious agents; and we are confident that emancipation and knowledge have enabled us to vanquish, completely, infectious disease. But let us examine the basis of our confidence. To be sure, there has been a tremendous increase in factual minutiae, but there is little basis for the idea that a genuine change has occurred in our fundamental concepts. For example, the idea still is strongly entrenched that the microbe is an active aggressor, and the host is a passive and innocent victim. It may be that we no longer admit to the laying on of hands, or to exorcisms to cast out the evil spirits. But today, as in the past, it is the unwanted and aggressive agent, be it evil spirit or microbe, that attacks the unaggressive host; and which, be it evil spirit or microbe, can be cast out or destroyed by appropriate means. The concept is difficult for us to accept that the host may be the aggressor, taking undue advantage of the reasonably peaceful microbe, many times, to be sure, to the host's own disadvantage. The concept is difficult for us to accept that infection may be a matter of ecology (if we may extend that field of biology to cover the influences which different species, when living together, have upon the environments and activities of each other) in which the host plays a major role; and in which individuals of one species or another may perish, and the balance may tilt in favor of one species or another, but the different species will continue to live together.

IMMUNIZATION AND VACCINATION

The concept is cherished almost universally, that antibody in the host leads to a condition that is incompatible with survival of the microbe, and that, consequently, infection can be eradicated by vaccination or other immunizing procedure. Faith in the concept is unshakable in spite of extensive evidence that infectious agents can survive for long periods of time in so-called "immune" populations and individuals. Actually, our faith makes it totally unnecessary for us to consider the immunogenic capacity of so-called immunizing materials. Moreover, our mere desire to do good invokes sufficient spell that the capacity to do harm is completely cast out of the materials. It is inconceivable to most of us that materials which are intended to do good, can do harm. Those points are well illustrated by our attempts to prevent rabies.

Rabies. The immediate stimulus to the present discussion came from newspaper accounts of difficulties encountered in Chicago by a physician who, because of dangers involved, had decided against rabies "vaccination" of a child bitten by

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a dog. The child developed rabies. The press accounts appeared at about the same time as did the following reports from the Weekly Disease Summary (1).

"Dr. G. E. McDaniel, South Carolina State Board of Health, reports that two children associated with rabies have died. In one instance a boy was bitten severely on the face by a dog which was proved to be rabid by laboratory examination. Anti-rabies vaccination was begun on the same day, and the child was given two doses per day for 14 days and one dose per day for the next seven. On the day of the last vaccination, the child was admitted to a hospital with possible rabies. He died two days later. The part of the brain sent to the State laboratory was not from the hippocampal region, and Negri bodies were not found. However, the brain was submitted to the CDC, Virus Laboratory in Montgomery, Alabama, where rabies virus was isolated. The other instance involved a girl who played with a dog that was killed the first week in December but was not examined for rabies. The child was not bitten, but antirabies treatment was recommended by her family physician. Treatment was begun on December 8 by the physician who gave her half doses daily for eight days. On the ninth day, the child was admitted to a hospital where a diagnosis of rabies vaccination encephalitis was made. The child died on December 21, following a sudden respiratory distress. The family refused an autopsy."

That arresting paragraph emphasizes both the unsatisfactoriness of the vaccine as an immunizing agent, and, vividly, the damage which can be evoked by the non-virus portion. A series of two cases could be ignored were they not representative of the total. Perhaps the time is long past when we, as immunologists, should have faced more courageously the problem of rabies.

DECLINE IN MORTALITY RATES

Tuberculosis. Figure 1 was prepared from well known data. They concern deaths from tuberculosis in England and Wales, and were taken

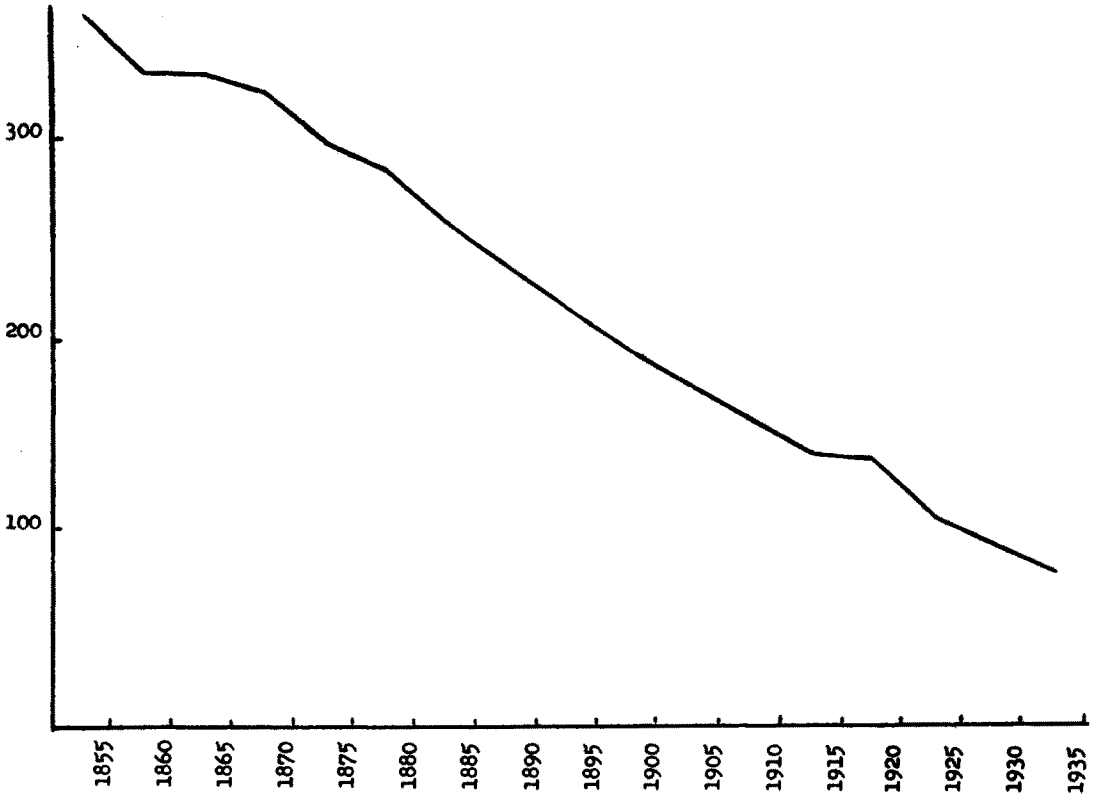

Figure 1. Mortality per 10^5 persons living in England and Wales 1851–1935. Data from Topley and Wilson (2).

from Topley and Wilson's *Principles of Bacteriology and Immunity* (2).

Why has the death rate for tuberculosis declined in a precipitous manner for more than one hundred years? The sociologists tell us it is the result of improved conditions of living. However, one, indeed, must be naive to believe that living conditions in the coal mines of Wales improved in the 1850 period! Furthermore, in America, during the period of time covered by the first portion of the graph, the death rate was rising steadily, not falling.

Tuberculosis is one of the diseases in which evidence is almost indisputable that the infectious agent persists in the immune host—or else we all in this room are dying of tuberculosis!

But let us turn to a subject fraught with less emotion and fewer semantics.

Diphtheria. Figures 2 and 3 are from a paper by W. W. Lee (3) in which data were presented showing that there was no change in the slope of the curve of diphtheria mortality rates in Philadelphia and New York City until about 1930. The chief purpose of Lee's paper was to show the effectiveness of an adequate vaccination program; that is, one which included vaccination of children of pre-school age. The paper illustrates the important, but neglected fact that even when a potent immunogenic material, such as diphtheria toxoid, is available, the material is ineffective unless properly employed. Also, the very excellent graphs illustrate neatly the decline in diphtheria mortality rather uninfluenced by therapeutic measures. It is not that that point has been unrecognized that I stress it, but rather that it has been ignored. Topley and Wilson, in perhaps the least unsatisfactory text in our field, referred to the same course of events in the London area as follows (4):

"Antitoxin came into general use about 1895, and the figures suggest that it had produced its full effect on the case-fatality rate about 10 years later; . . . But, if we are disposed to be critical, we shall note that the downward trend had shown itself before the introduction of antitoxin."

The figures referred to begin with the year 1889 which was six years before the introduction of antitoxin. During that six-year pre-antitoxin period the case-fatality rate declined from 40.7 to 22.8. During the six-year post-antitoxin period the rate declined from 22.8 to 11.1. Perhaps, it might be well for more of us to be "disposed to be critical"!

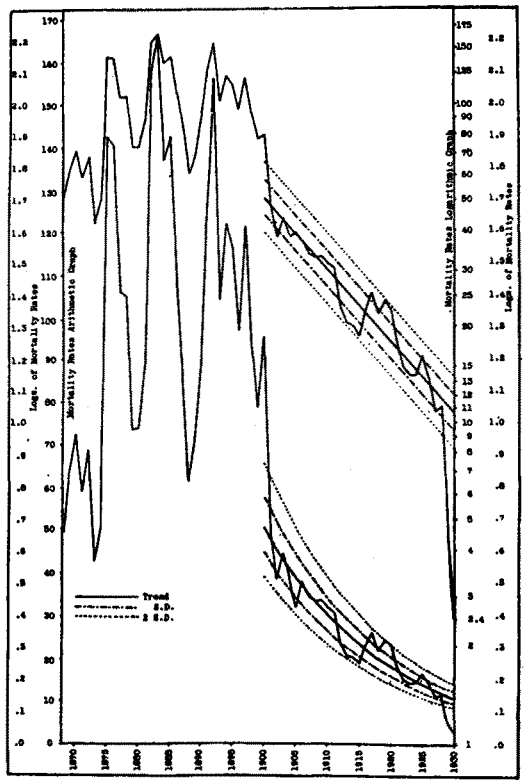

Figure 2. Diphtheria mortality rates in Philadelphia plotted as in Figure 1. The trend is fitted to the exponential formula $y = ab^{-x}$ in the arithmetic graph and to the formula $log.\ y = log.\ a - x(log.\ b)$ in the semilogarithmic graph. The S.D. lines in each graph correspond, in the lower graph plotted as numbers, in the upper plotted as logs. Reproduced from Lee (3).

Onset of the cycle of clinically recognized diphtheria. Lee's graphs suggest that the decline in diphtheria mortality rates for New York and Philadelphia began between 1875 and 1880; and that previously the rates had been increasing. That is, the course of events appears to have been part of a cycle. The time of onset of the cycle is clearly indicated in the literature.

The data included in Table I were taken from a "Historical Note" by C. F. Bolduan, which was included in a pamphlet published by the New York City Health Department, under the title "How to Protect Children from Diphtheria" (5). According to those data (Table I) the first recorded death of diphtheria occurred in 1857, and during the subsequent eight years, the number of deaths per year increased rapidly.

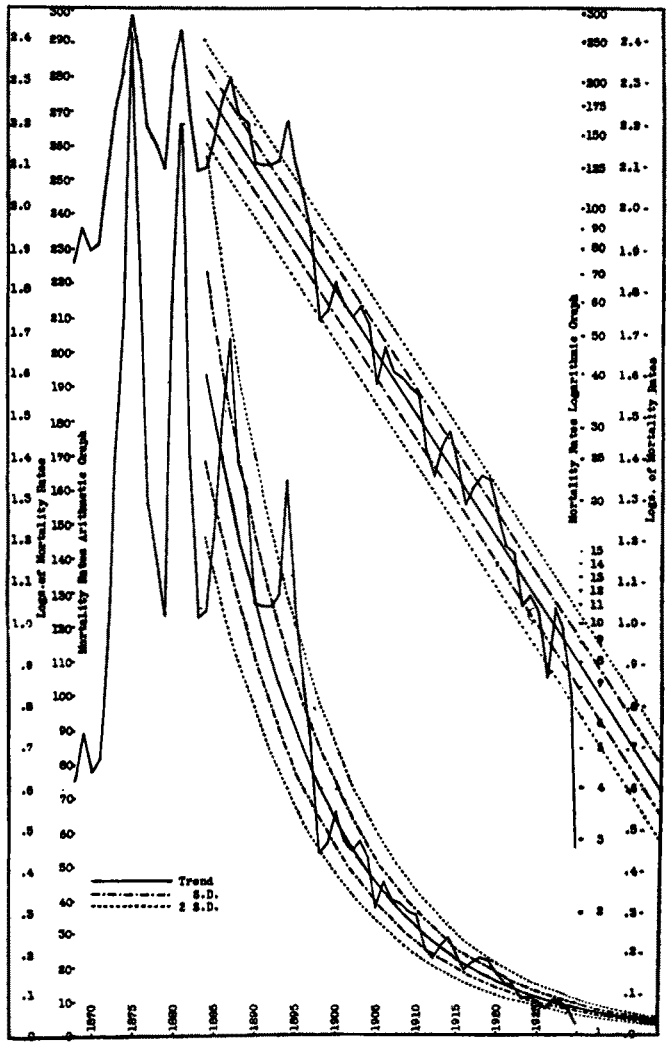

Figure 3. Diphtheria mortality rates in New York City. Upper graph semilogarithmic, lower graph arithmetic. Trend fitted to the exponential formula $y = ab^{-x}$ in lower graph, and $log.\ y = log.\ a - x(log.\ b)$ in upper graph. S.D. lines in each graph have corresponding values. Reproduced from Lee (3).

Many physicians, and others, were of the opinion that diphtheria appeared as a new disease during the middle of the 19th century. But Frost (6) assures us, as follows, that such was not the case:

"... we have no very reliable statistics of either prevalence or mortality prior to 1850 or 1860. It is evident, however, (1) that the disease was geographically widespread and (2) that it was less prevalent and less fatal than it later became. At the same time, the disease showed indications of increasing epidemic tendencies. From 1800 to 1850 more or less localized epidemics of malignant diphtheria were occurring from time to time, especially in France. Then, between 1850 and 1860, there developed, apparently from a focus in France, a great pandemic, sweeping within a decade over the world. In western Europe and the United States, the regions for which we have the best records, diphtheria became much more prevalent and much more malignant, in so much that the practitioners of the day often spoke of it as a 'new' disease. Its mortality rose to extraordinary heights, which, with considerable fluctuations, were sustained for twenty-five to thirty years, that

TABLE I

Deaths probably diphtheria, City of New York, 1851–1865 inclusive

Year	Inflammation of		Quinsy	Sprue	Ulceration of Throat	Angina	Croup	Diphtheria	Totals
	Throat	Tonsils							
1851	53	—	—	78	5	38	462	—	636
1852	50	—	—	33	20	43	595	—	641*
1853	107	—	—	43	5	16	502	—	673
1854	118	23	—	90	12	10	637	—	772*
1855	64	13	—	66	10	12	639	—	804
1856	50	8	4	49	7	14	550	—	682
1857	71	15	10	36	7	21	560	2	622*
1858	70	15	2	56	7	11	478	5	644
1859	111	4	3	24	19	58	622	53	894
1860	132	—	6	15	—	37	599	422	1211
1861	101	—		25	17	16	460	453	1072
1862	68	—		27	7	2	685	594	1383
1863	49	—		14	25	64	908	981	2041
1864	18	—	1	4	8	37	754	781	1603
1865	—	—	—	4	24	5	449	534	1016

* Discrepancies included in original.

is, until about 1885 or later, when a consistent decline began."

What caused the dramatic changes described by Frost? The sudden increase in mortality cannot be attributed to sudden introduction of a new agent. The sudden decrease in mortality cannot be attributed to specific therapy. But let me continue from Frost's discussion:

"To what may we attribute this sudden and widespread increase in the prevalence and malignancy of diphtheria in the middle of the last century? Was it due to a correspondingly great increase in prevalence of infection with the diphtheria bacillus, or was it due to a change in the ratio of disease to subclinical infection? These questions cannot now be answered with certainty, but it is at least a plausible hypothesis that the essential difference between the epidemic and the pre-epidemic periods lay, not in the prevalence of infection (or not in this alone), but in a different balance between subclinical infections and those which came into the zone of clinical recognition. Facts which especially suggest this explanation are that, before the pandemic, diphtheria was already geographically widespread; that the increase in prevalence was accompanied by a change in the clinical character of the disease, and finally, that at present, in cities where *infection* with the diphtheria bacillus is demonstrably almost universal, we have no such high morbidity as resulted in the epidemic period."

Basically, Frost is pointing out that an inverse relationship exists between *clinical* diphtheria and the prevalence of *C. diphtheriae*. That is to say, when the etiologic agent of diphtheria is widespread in the community, the community is "immune" to the clinically recognizable disease!

Why do immunologists ignore those facts?

Before continuing the discussion I wish to point out that each time I discuss this subject I am accused of being, among other things, a therapeutic nihilist. My discussion has nothing to do with therapy—I leave therapy to others—it has to do with what, in my opinion, should be the immunologist's interest in ecological relationships. But a word as to therapy. It is my opinion that had diphtheria antitoxin been used *properly*, when introduced, there would have been the same kind of abrupt change in mortality rates in 1895 which Lee showed to have occurred about 1930, following the *proper* use of toxoid.

Measles. Figure 4 was prepared from data presented by Brincker in his paper (7), "A Historical, Epidemiological and Etiological Study of Measles," and shows the mortality rates per 10^6 in the County of London over the period 1851 to 1936.

The data require no discussion other than that necessary to emphasize the point that the decline in deaths resulting from measles occurred without the aid of specific therapy, for none was available either for measles, as such, or for complicating pneumonia.

Greenwood and his associates (8) discuss the problem of measles as follows:

". . . our observations, and the interpretations that we have placed upon them, are in general accord with the view expressed by Hamer (1906) that the periodicity of such an epidemic disease as measles is probably due to periodic changes in the constitution of the population exposed to risk, leading, after each epidemic wave, to a gradual re-accumulation of susceptibles. . . . In the natural world, taken as a whole, the re-accumulation of susceptibles is by births rather than by immigration; but there are specialized herds, such as schools in general and boarding schools in particular, in which, as Dudley's observations have so clearly shown, the immigration of non-immunes term by term is probably a decisive factor in determining the course of events.

"In any of those common endemic-epidemic dis-

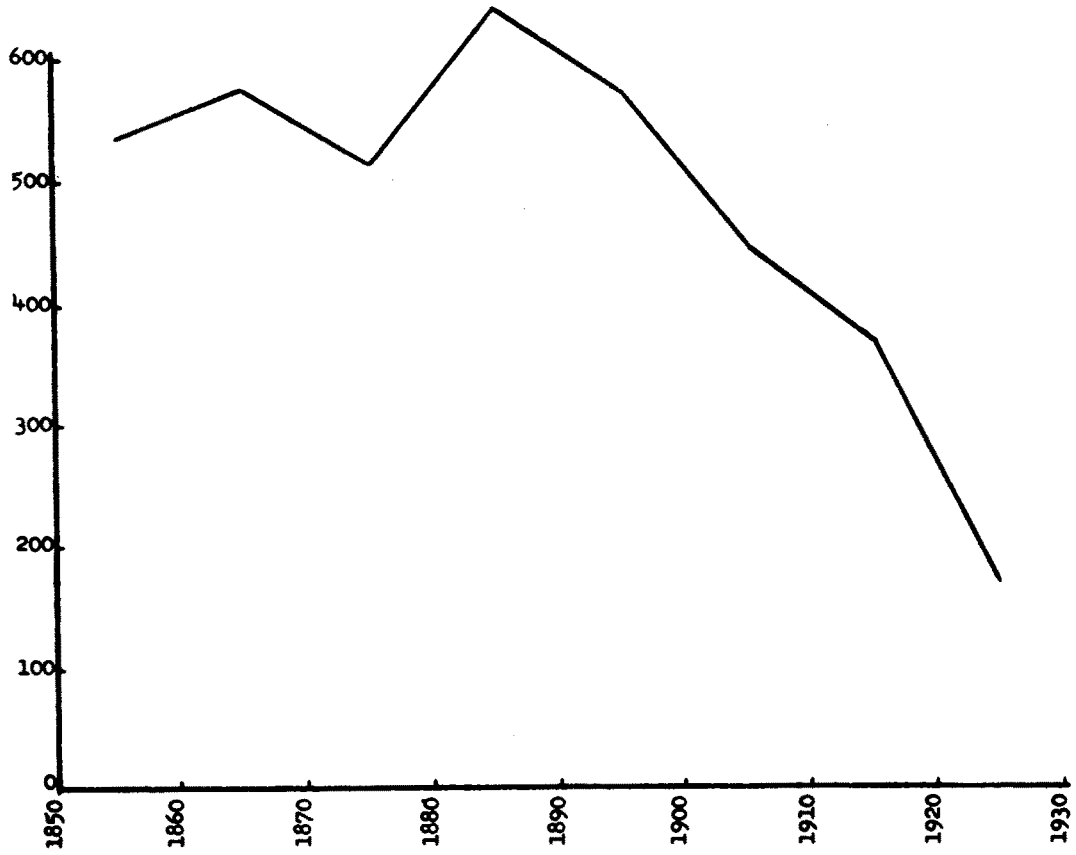

Figure 4. Death-rate of measles per 10^6 of population, London, 1851–1930. Data from Brincker (7)

eases from which many or most of our people suffer at one time or another during their lives, but which occur in epidemic form only at more or less widely-spaced intervals, we should regard this ever-varying state of the immunological constitution of the herd as the main factor determining the intervals at which the epidemic waves occur."

Pneumonia. My discussion, thus far, has dealt with rabies, tuberculosis, diphtheria, and measles. But, what of the infections which have been so miraculously eradicated by the sulphonamides and by the antibiotics? Permit me to select pneumonia as being representative of that group.

In order to present unprejudiced material, Figure 5 was prepared from a photographic copy of a chart which was included in a pamphlet entitled "The Pneumonias, Management with Antibiotic Therapy" (9) and distributed recently by one of the world's largest producers of antibiotics. The data deal with New York State.

It is clear from the data (Figure 5) that the rapid decline in pneumonia death-rates began in New York State before the turn of the century and many years before the "miracle" drugs were known. Certainly, it would not be facetious to suggest that no one in the room has sufficient therapeutic faith to argue that the drugs available to physicians at the turn of the century were sufficiently potent to have initiated the precipitous drop in mortality.

If we are disposed to be critical, we shall note that the steep downward trend in the pneumonia death-rate (Figure 5) began to taper off in the early 1940's and that during the past few years the curve has followed a more or less horizontal course. It is of considerable interest that the initiation of that course of events coincided with the introduction of the antibiotics, and that the decline in death-rate essentially ceased as those agents became more and more universally employed. Are we to infer that those valuable

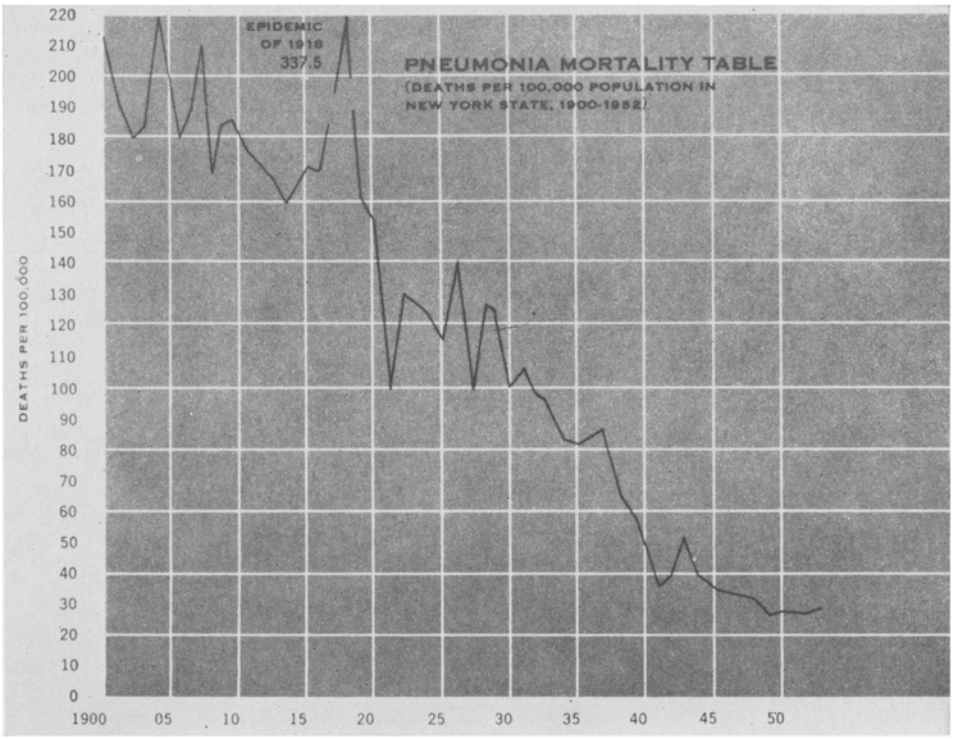

Figure 5. Curve compiled from 70th Annual Report of the New York State Department of Health and Monthly Vital Statistical Reviews from the same source. New York State was selected as representative of the decline in pneumonia mortality over the last 50 years because of the relative accuracy of the statistics compiled by the New York State Department of Health. Reproduced from *"Pneumonias, Management with Antibiotic Therapy"* (9).

agents have worsened the situation? I think not. It would seem to be a more logical conclusion that during recent years, quite regardless of our therapeutic efforts, a state of relative equilibrium has established itself between the microbes and the "every-varying state of the immunological constitution of the herd"—a relative equilibrium which will continue, perhaps, just so long as it is not disturbed, unduly, by biological events

THE CONQUEST OF DISEASE

The physician or the medicine man of each age has attributed the control and cure of disease during his own particular era to the therapeutic procedure then in vogue. The possibility that infection is a biological phenomenon dealing chiefly, perhaps, with ecological relationships escaped the past, as it has escaped the present. Hirsch (10) discusses the case of scarlet fever as follows:

"In the year 1801 (says Graves) scarlet fever committed great ravages in Dublin, and continued its destructive progress during the spring of 1802. It ceased in summer, but returned at intervals during the years 1803–4, when the disease changed its character; . . .

". . . The long continuance of the period during which the character of scarlet fever was either so mild as to require little care, or so purely inflammatory as to yield readily to the judicious employment of an antiphlogistic treatment, led many to believe that the fatality of the former epidemic was chiefly, if not altogether, owing to the erroneous method of cure then resorted to by the physicians of Dublin, who counted among their number not a few disciples of the Brunonian school. . . . The experience derived from the present epidemic (1834–5) has completely refuted this reasoning, and has proved that, in spite of our boasted improvements, we have not been more successful in 1834–35 than were our predecessors in 1801–2."

The shift from the endemic state to the epidemic state and from the epidemic state to the endemic state can be traced over long periods of time for many of the infectious diseases. It is unscientific, indeed it is stupid, to ignore indisputable data merely because we choose to accept blindly the dogma of immunity—that the infectious agent cannot and does not survive in what we choose to call the immune or the immunized host, that the *clinically* uninfected herd cannot be the reservoir for the epidemic by which it is decimated. That the host can be, and is, the reservoir can be well illustrated by Brill-Zinsser disease. In that instance the typhus fever rickettsia survives in the immune host for many years; the rickettsia serves not only as the source of the recrudescence, but, doubtless, serves also as the stimulus to the immunity. It is possible that that is the pattern of endemic-epidemic disease.

Perhaps the immunologist, by being somewhat less of a serologist, might investigate what Greenwood refers to as "the every-varying state of the immunological constitution of the herd" and at the same time investigate the ecological conditions under which the microbe stimulates that ever-varying constitution, yet, at the same time manages to survive and to continue the cycle of immunity followed by clinically recognized disease.

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