

PART I. KEYNOTE ADDRESS

EPIDEMIOLOGY OF AIRBORNE INFECTION

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In the perspective of the past 100 years the concept of airborne infection has had a rather turbulent history.¹ Interest in it, on the part of scientists and the public, has swung in the extreme. Prevailing attitudes toward the importance of airborne infection have often been stronger, either pro or con, than the evidence at hand has justified. Undoubtedly we are in such a phase right now with the general underestimation of the importance of the subject.

A limiting factor in the more orderly development of this field, in contrast to other fields of environmental sanitation such as the waterborne and foodborne infections, has been the lack of a sound theoretical basis. Rather than developing from a series of hypotheses based on epidemiological observations and tested repeatedly in the laboratory and in the field, there has been a tendency to empiricism and to overgeneralization from limited observations. The field of airborne infection has had no John Snow to lay down sound theoretical principles early in its development.

In the past 25 years, however, and more particularly in the past 10, this field has taken on new directions and broader scope. Whereas 25 years ago there were few who claimed any importance for this field, now there is a series of diseases in which the airborne route of infection has been well substantiated. Several broad principles have become established which are based on physical, physiological, and microbiological laws and backed by quantitative experimental measurements. Together these constitute, in my opinion, an adequate basis for a Theory of Airborne Infection.

Such a Theory, if well laid, is crucial to the logical development of the field. It will serve to guide future research work and permit discrimination in the development, evaluation, and use of proposed control procedures. A primary objective of this Conference should be the examination of these principles and an assessment of the de-

¹ References 2, 5, 15, 16, 18, 19, 23, 27, and 29 represent general reviews of this subject.

gree to which they may be considered sufficiently general to be included as part of the Theory of Airborne Infection.

As my contribution to the opening of this Conference, I propose to discuss the historical background briefly, to propose a definition of terms, and to summarize the epidemiological evidence for those diseases that are now known to be airborne in nature.

HISTORICAL BACKGROUND

Prior to the time of Koch and Pasteur, airborne infection was the prevailing concept of the spread of infectious diseases. The terms "miasm" and "malaria," meaning noxious vapor and bad air, reflect this attitude. The great epidemiologist and statistician, William Farr (9) in the British Registrar General's office, produced an extraordinary epidemiological confirmation of this hypothesis during the great cholera epidemic of 1849 in London. He began with the assumption that the source of the cholera poison was the Thames River and that this poison diffused over the city in relative proportion to the elevation of the various areas of the city. Knowing the cholera mortality for each subdistrict, he grouped these according to their elevation and observed the correlation shown in Fig. 1.

Thus by accepting a prevailing scientific concept of his day and using the tools available to him, he found a confirmation that I believe would be impressive to any scientist at any time. He was so close and yet so far from a true understanding. John Snow, working contemporaneously and in collaboration, produced a better and more sophisticated hypothesis. To Farr's credit, he accepted Snow's findings and acted upon them.

Farr's correlation stands as a sobering symbol and perhaps serves as a useful reminder to us at this Conference. How much of what we think we know is less well founded than Farr's hypothesis was in 1849? How many of us will be as magnanimous and broad minded to accept new evidence as Farr was to accept Snow's?

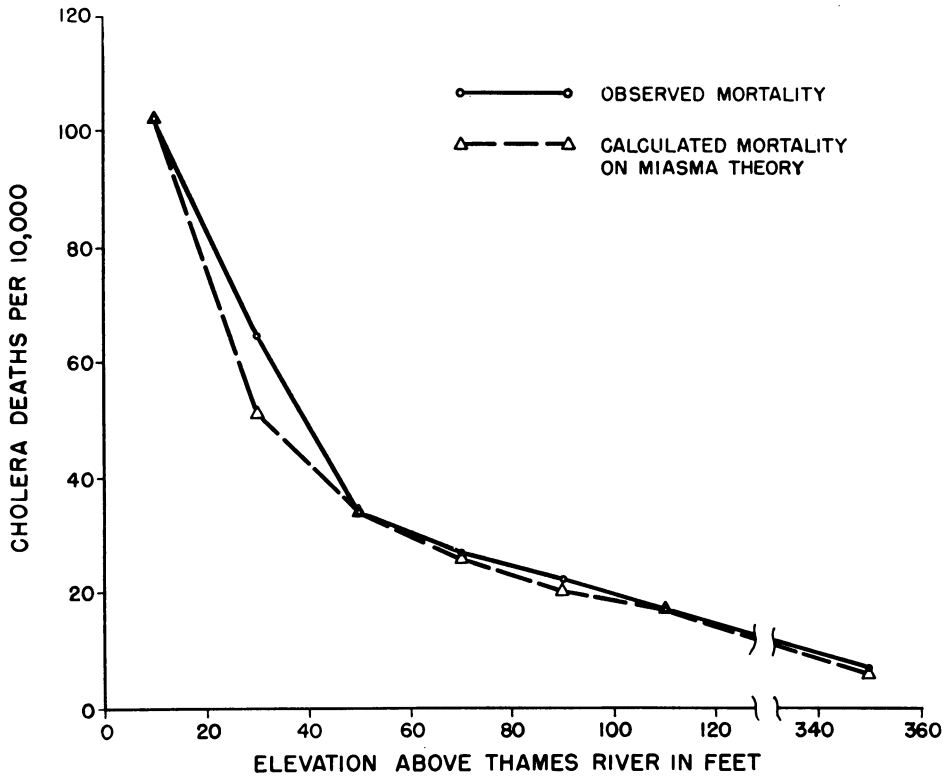


FIG. 1. Correlation of cholera mortality and elevation above the Thames River, London, 1849

With the advent of the bacteriological era, miasms and malarias were discarded for a far more comprehensive theory of infectious disease. The work of Lister, moving rapidly from antiseptic to aseptic surgery, and the extension of these principles to the isolation of contagious diseases in hospitals established the importance of contact infection in the incontrovertibly dominant position it holds to this day.

It is difficult to challenge the basic discovery of asepsis. This made modern surgery a reality and permitted the maintenance of pediatric hospitals. Too often when the principles of asepsis are ignored, serious trouble has followed inexorably. The valid question, therefore, is not whether contact infection or airborne infection is important but rather does airborne infection play any role. It is also valid to question whether observations based largely on hospital experience are generally applicable in the community, in schools, and in other special circumstances such as Army barracks and institutions.

Chapin (5, 6), from his meticulous observations

of childhood contagious diseases in Providence, believed that contact was all important in the community. It is worthy of note, however, that in his rather sweeping claims for contact infection he specifically excluded tuberculosis, which he admitted might be airborne in its spread. Chapin led the campaign for a rational approach to the control of infection. He fought against the archaic practice of terminal fumigation. Undoubtedly his influence contributed to the loss of interest in airborne infection. Whatever the reasons, interest waned for more than a quarter of a century.

In 1934, William Firth Wells (25), working first at Harvard School of Public Health and later in Philadelphia, developed the concept of the droplet nucleus and challenged the essentially exclusive dominance of contact infection. He demonstrated that a variety of pathogens, including streptococci, pneumococci, coliform organisms, and influenza virus, could be atomized into a chamber and remain viable in the resulting aerosols for hours or even days.

He extended his ideas to the hypothesis that

the droplet nucleus was the primary mode of spread of measles and other contagious diseases and proceeded to test his ideas by installing ultraviolet lights in school rooms in and about Philadelphia. His first trial was a notable success. Later trials were less dramatic.

In 1940, Dr. O. H. Robertson (22) and his group at the University of Chicago began comprehensive studies both in the laboratory and the field on the use of glycol vapors and dust suppression for controlling cross infections in hospitals and epidemic respiratory diseases in Army barracks.

Concurrently with the work in this country, interest in the question of airborne infection reawakened in Britain. The extent of environmental contamination with diphtheria bacilli and streptococci was recognized and its significance was studied in detail. Great concern was also felt over the risk of airborne infection among the populations crowded into bomb shelters during World War II (1).

All of this new work and interest in airborne infection constituted a substantial challenge to the contact theory. During and subsequent to World War II, a large number of field trials were undertaken to test ultraviolet irradiation, glycol vapors, and dust suppression in the control of acute respiratory diseases and β -hemolytic streptococcal infections. The final result of all these studies was one of discouragement. The beneficial effects, if any, were only partial; the engineering complexity of maintaining effective air disinfection seemed insuperable (2, 15, 21, 23). Furthermore, during and subsequent to this period, increasingly detailed epidemiological studies pointed more and more toward the importance of close personal association rather than the air in the spread of this group of infections in hospitals and barracks (29). Thus, the challenge to contact spread of infection failed.

While this discouraging experience was being accumulated, a great deal of basic work on the precise mechanisms of contact and airborne infection was taking place. These mechanisms were being subjected to quantitative scientific scrutiny as never before. Many discoveries of great consequence have been made both in the laboratory and the field. These include:

1) The underlying principles of generation of microbial aerosols both from artificial and natural sources.

2) Techniques of sampling microbial aerosols and of exposing both animals and man under experimental conditions.

3) The great variation in the capacity of different infected persons to contaminate their environment and to serve as dangerous carriers or spreaders.

4) The extraordinary capacity of certain routine laboratory procedures to set up fine-particle aerosols and thus infect laboratory workers through inhalation.

5) The discernment of the precise points in the upper and lower respiratory tract that may serve as portals of entry of infection and the great variation of the dosage required to infect at these different sites.

6) The crucial importance of particle size in determining penetration and retention of inhaled particulates.

These subjects cannot be considered in detail here. They will occupy the attention of this Conference for the first full day. They are general in scope. They apply to many infections, not just to single, specific ones. Many are well-established principles based on physical laws, known anatomical facts, and physiological mechanisms, supported by abundant experimental and epidemiological data. This is the stuff of which the Theory of Airborne Infection must be made.

DEFINITIONS

Much confusion has arisen in this field over terminology. Some agreement on a definition of terms is desirable. There are four essential mechanisms of spread commonly discussed when contact and airborne infection are considered. These are:

- Contact
- Droplets
- Droplet nuclei
- Dust

The term "contact" in this sense offers little difficulty. It means contiguous touching either directly as in kissing or indirectly as in the use of contaminated surgical instruments, shaking hands, or the passing of a toy from child to child.

The term "droplets" offers the most trouble. These emanate from the mouth and to some extent from the nose during talking, coughing, and sneezing. Sixty years ago, Fluegge showed that these droplets extend not more than about one meter from the mouth. The large droplets fall to

the floor, the smaller ones dry to form small residues, and many remain suspended in the air for long periods of time. Thus, droplets actually pass through the air and in a literal sense are airborne but at the same time they exist only in the immediate vicinity of their source.

"Droplet nuclei" are the small residues arising from the dried droplets that remain suspended, and may be wafted, on air currents to the far corners of the room or passed through ventilating ducts.

"Dust" is composed of the usually large particles that exist on the floors, clothing, or bedding and that may be periodically suspended and re-suspended in the air by human activity, especially dressing, sweeping, or bed making.

Although it was common practice in this country 20 years ago to consider droplet infections synonymous with airborne infection and even though the British still favor this use of the term (29), there are valid reasons against it. As Chapin emphasized, droplets exist only in the close vicinity of the infected person. Control of such droplets entails such actions as covering a cough with a handkerchief and the wearing of a mask in conformity to the simple principles of good personal hygiene. The approach to the control of droplets, therefore, is similar to the control of contact.

On the other hand, the control of both droplet nuclei and dust is amenable to the engineering approaches of controlled ventilation, ultraviolet irradiation, disinfectant vapors, and dust suppression. For these reasons, it is recommended that droplet infection be classed as one form of contact infection and that the term airborne infection be limited to spread by droplet nuclei and dust.

EXAMPLES OF AIRBORNE INFECTION IN NATURE

The second full day of the Conference is devoted to the discussion of specific bacterial, viral, and fungal diseases in which the airborne mode of spread is an important factor. Most of these reports deal with carefully conducted experimental studies in animals or in man. Particular emphasis is placed on pathogenesis. This illustrates the change that has taken place, particularly in the past decade, in the study of airborne diseases. Less effort is being directed to large controlled field trials in situations where the evidence of the importance of airborne infection is

weak, and more effort is being spent to define the precise mechanisms where airborne infection is known to be important.

Concurrently, with these experimental approaches there have been a number of careful epidemiological studies of localized outbreaks where the existence of an airborne mode of spread seems to have been well established. None of these can be reported in detail and only a few will be reported on tomorrow. It is pertinent, therefore, at this time to comment on a few illustrative examples in brief narrative form.

Psittacosis. The familial outbreaks of psittacosis that have been repeatedly described since 1930 represent a classic type of epidemiological story favoring airborne infection. These characteristically develop following the acquisition of a parakeet or other psittacine bird into the home. The usual circumstances where the bird remains inside a cage, becomes ill, soils its feathers with cloacal discharges, and sets up an infectious aerosol by ruffling its feathers seem reasonably consistent with the airborne mode of spread.

More extensive evidence of airborne psittacosis is found in the repeated outbreaks among employees of turkey-processing plants and rendering plants in Texas and Oregon.

As reported by Irons, Denley, and Sullivan (14), five outbreaks comprising at least 96 cases and 7 deaths occurred among employees of two poultry-dressing establishments between 1948 and 1953. Three of these outbreaks were of the characteristic common source type with exposure being traced to the processing of a single flock of turkeys on a certain day. The highest attack rates, over 50%, occurred among those who killed the birds and picked the pinfeathers; lowest attack rates were found among the eviscerators; the graders and packers working in separate rooms escaped infection entirely. In such an intrinsically messy industrial process it is obviously difficult to distinguish between contact and airborne infection, but the explosive nature of the outbreaks and the high attack rates suggest that airborne infection played an important role.

During the winter and spring of 1955-1956 in Portland, Oregon, 33 serologically confirmed cases and 54 probable human cases of psittacosis were recognized (20). Of these, 28 cases were hospitalized and 2 were fatal. The cases were associated with three large flocks of turkeys either through contact on the farm or in processing plants or at

rendering plants. Extensive epizootics due to a highly virulent strain of psittacosis virus occurred among the turkeys. The most significant fact of this epidemic to this Conference was the outbreak in one of the rendering plants. Between the 26th of January and the 9th of March, 26 cases of psittacosis or psittacosis-like disease occurred among the 38 employees of this plant. Cases occurred in all types of workers except the truck drivers. Dead turkeys in large and small numbers were brought to the plant several times a week. These birds came from one of the large flocks that was experiencing a severe epizootic.

The process used in this rendering plant was to chop the whole bird, feathers and all, into small bits in a rotary chopper and then blow the material through a wide diameter duct into a vat for steam pressure cooking. The opportunity to produce an infective aerosol is obvious.

The airborne character of these outbreaks seems evident. The remarkable feature of them is their apparent rarity. In view of the extent of psittacosis virus in turkeys and other fowl and of the crude methods used in poultry dressing and rendering plants, why are such epidemics not more frequent?

Q fever. Sir Macfarlane Burnet (4), in his early studies of *Q fever* in Australia, clearly stated that the mode of spread of the cases, associated with a certain abattoir, must be airborne in origin. Late in World War II, however, when many sizable epidemics occurred among troops in the Italian campaign, the many investigators were reluctant to accept an airborne mechanism. In the Grottaglie outbreak involving one-third of 1,638 Air Force personnel, the epidemic was clearly common source in character (7). It involved five different squadrons housed along the full length of a 6,000-ft air strip. The incidence rates and epidemic curves were essentially identical in all groups, indicating some common simultaneous exposure. After a searching, epidemiological inquiry in which the present author was an active participant, no conclusion as to the origin or mode of spread could be reached. It was recorded that goats and sheep were herded in nearby fields and for 2 days prior to departure all the troops slept in the open. It was finally assumed that some unidentified insect vector must have been responsible. Even though the airborne character of laboratory epidemics of *Q fever* was known at this time, the investigators were reluctant to accept

the concept that an infective aerosol cloud could diffuse over such a wide area and result in so much disease.

The subsequent studies of Lennette and his co-workers over the past decade have fully dispelled this reluctance (28). Not only have a series of epidemics of obviously airborne origin been fully described, but the source of the agent in high concentration in the placentas and lochial discharges of sheep and goats has been demonstrated.

Recently in California a most dramatic outbreak of *Q fever* has been reported (24). Mr. Clyde Wellock, a senior medical student, studied a group of 75 confirmed cases of *Q fever* in Oakland and neighboring cities in the San Francisco Bay area in the spring of 1959. Almost all of these resided in a narrow triangular swath 7 miles long and $\frac{1}{2}$ to 1 mile wide that began in the city of Emeryville near the foot of the Bay Bridge and ran southeasterly through the city of Oakland and on into Alameda. The few cases which resided outside the swath had histories of regular employment or frequent visits to locations within the swath. The direction of the swath was in line with the almost constant prevailing wind in that area. At the head of the swath was a rendering plant where sheep and goats and occasionally the placentas from these animals were processed. The incrimination of this rendering plant as the source of an infective aerosol that traveled several miles down wind is apparent. Just how and when the infective aerosols were created is not yet certain.

Pulmonary mycoses. Coccidioidomycosis from the time of its first recognition as a common and widespread infection in the desert areas of the West has presented obvious characteristics of an airborne infection. The outbreak among Stanford University students in California (8) and the extensive studies directed by Smith to control the infection at military bases during World War II clearly indicate that the dustborne origin was recognized early. Dr. Smith will consider this subject more fully.

Histoplasmosis was recognized as a widespread infection somewhat later. Early studies were concentrated on a geographical localization of histoplasmin skin sensitivity and pulmonary calcification. Definition of the manifold clinical characteristics of this disease and its intrinsic airborne origin has been achieved only during the past 10 years. Now there is no question of the extent and

importance of this airborne disease. Dr. Furcolow will consider this subject more fully.

Other pulmonary mycoses, notably blastomycosis, seem most logically to be airborne in character but the evidence to support this assumption is still elusive.

Anthrax. For years anthrax has been considered a rare cutaneous disease associated with certain hazardous industries that process coarse wool and goat hair. The disease also is a minor hazard to agricultural workers. Contact infection by the introduction of the spores through a break in the skin is the logical mode of infection.

Woolsorter's disease, the pulmonary form of the infection, was described late in the 19th century but has been so excessively rare in modern times as to be discounted. But in Manchester, New Hampshire, in 1957, an outbreak of five cases of inhalation anthrax, four of them fatal, occurred during an interval of 10 weeks (3). The cases tended to concentrate among the dustiest occupations in a goat-hair processing mill. The extent of the contamination of the air with anthrax spores, many in the particle size range below 5μ , clearly indicated the airborne nature of the infection. The most remarkable feature of this epidemic is the lack of any definitive explanation of why it occurred. Contamination of all goat-hair mills is the general rule but no other outbreak such as this has been reported in this country.

Brucellosis. Since the work of Hardy, brucellosis in Iowa has been recognized as a special hazard of slaughterhouse workers and of the men on the farms who butcher animals. The hazard apparently does not affect their wives and children who drink raw milk. The generally accepted mode of spread was contact. In the winter and spring of 1960, however, an outbreak of 128 cases in a large slaughterhouse in Iowa that employs more than 1,000 workers was studied by personnel of the State Health Department and the Communicable Disease Center (11). A regular endemic occurrence of brucellosis, four to eight cases per year, had been recognized as a difficult problem at this plant. Thus the incidence in 1960 was a sharp increase. Some of the highest attack rates occurred among the employees working in the kill room. Many of these men had close contact with the animals and with fresh tissues and tissue fluids. There were, however, four cases among the rosin pullers, who wear protective clothing and

remove hot rosin from the unopened carcasses after they have been dipped in a vat maintained at 310 to 325 F. The circumstances of this outbreak strongly point to airborne infection.

Pulmonary tuberculosis. Incomparably the most important airborne infection is pulmonary tuberculosis. It is difficult to determine when this crucial feature of this disease became broadly recognized but it is evident that its full significance is yet to be appreciated.

Koch demonstrated aerial infection with tubercle bacilli in 1884. The concept that tuberculosis could be acquired by inhalation is unquestionably old. But the ideas of Fluegge have dominated our thinking, namely that infection can occur only in the near vicinity of the patient. The dominant view for the first half of this century was clearly the importance of close, prolonged, intimate contact including droplet infection. The more precise mechanism of the inhalation of single droplet nuclei that can now be visualized was not appreciated until quite recently.

Wells, Ratcliffe, and Crumb (26) gave the first clear statement, supported by experimental data, of the crucial importance of particle size in the infection of the rabbit lung by inhalation. Wells showed that small particles, essentially single bacterial cells, could infect by inhalation, whereas large particles containing viable cells failed to do so. Lurie et al. (17) extended this work in a comprehensive manner showing that each infective particle inhaled and retained in the alveoli produces a separate tubercle. Thus Lurie has reached the logical end point in this infection, namely, that the infectious dose is a single organism in the right place.

The classic experiments of Riley, to be reported at this Conference, further substantiate the keen insight of Wells' precise thinking on the mode of spread of tuberculosis.

Epidemiologically, the dominant concept in tuberculosis control has been, and to a large degree still is, the importance of close contact. Yet, in my opinion, the mass of the evidence is far more consistent with the concept of airborne infection. Household contacts and even marital partners of sputum-positive patients often fail to become infected. At the same time, numerous epidemics of tuberculous infection have been recorded where essentially everyone in a group became instantaneously infected (10, 12, 13). These

observations are much more consistent with the hypothesis that only certain tuberculous individuals act as effective disseminators and these do so probably intermittently and only under certain circumstances. It is logical that the critical feature of these tuberculous disseminators is their capacity to produce viable aerosols of small particle size.

Laboratory-acquired infections. In this discussion essentially no mention has yet been made of the large and increasing experience with airborne infections in laboratories. This subject will be fully covered by Drs. Sulkin and Wedum. It needs no attention here except to emphasize that the extent to which modern laboratories are equipped with elaborate and expensive safety devices is monumental testament both to the respect now being shown for airborne infection and to our understanding of the mechanisms of its occurrence.

Hospital-acquired infections. Little mention also has been given to the modern experiences with hospital-acquired infections that are so much the center of interest at the present time. Included in this group are not only the surgical wound infections but epidemics of infant diarrhea, staphylococcal infections, and other bacterial and viral infections that spread through hospital wards. Some of these outbreaks have occurred under circumstances that strongly suggest the airborne route of infection as Dr. Eichenwald will report, but most of these problems seem to relate more closely either to contact with the infected person or with contaminated objects rather than to contamination of the air.

CONSIDERATIONS REGARDING PARTICLE SIZE

Perhaps the most important single principle to come to wide recognition during the past two decades is the relation of particle size to penetration and retention at various levels of the respiratory tract. As Professor Hatch will report, only those particles in the size range below 5μ can penetrate readily to the alveoli.

Abundant experimental evidence has now accumulated to show that one of the general characteristics of the infectivity of small particle aerosols is the extremely low dose required. As with Lurie's work in tuberculosis, experiments show that many other agents are approaching the limit of one or a very small number of viable organisms necessary to infect. Plague and anthrax appear to be two notable exceptions to this principle.

It is of special interest that the airborne diseases recounted above are ones in which the portal of entry is the alveolus of the lung. Thus, small particle aerosols must have been involved in these outbreaks.

The recognition of these new concepts helps to explain some of the confusing epidemiological observations that have been mentioned. The rarity of outbreaks of psittacosis, brucellosis, and Q fever, in spite of the obvious and almost continual contamination of abattoirs and rendering plants, may be explained by the assumption that truly small infective particles are probably very rarely produced. To produce particles small enough to reach the alveoli, that is, essentially single bacterial cells, requires unique circumstances that rarely exist in nature. Such small particles can be produced artificially from the liquid state only by the application of considerable forces to very small orifices, using dilute suspensions. The crude splashing or grinding of highly viscous fluids or tissues would be unlikely to produce small enough particles to be infective. Thus, to account for the outbreaks that are reported, it is necessary to postulate special features or circumstances that yield unusually fine aerosols. What these hypothetical conditions may be is not clear. They should be searched for in future epidemics.

The pulmonary mycoses present a different set of circumstances. These fungi grow and sporulate in the form of small particles that can readily reach the alveoli of the lung. Hence, the high rates of infection in the endemic areas are readily understandable.

The problem of how tuberculosis infection of the human lung occurs is of special interest. All that is necessary to produce a human infection is the inhalation of a single tubercle bacillus once in a life time, yet at the present time in this country less than 5% of young adults have been exposed to this hazard during the past 20 years. Obviously the spread of tubercle bacilli in the general population has essentially ceased in spite of the tens of thousands of open cases that are known still to exist. What are the reasons?

It is probable that highly specialized conditions must be met before an infected tuberculous person can act as an effective spreader. The usual tuberculous sputum is not suitable for producing fine aerosols by the normal actions of coughing or expectoration. Some special conditions must

exist. These should be sought for and defined. Valuable control measures might follow logically.

With regard to the laboratory-acquired infections, it is clear that many artificial procedures such as blowing the last drop from a pipette and using centrifuges and blenders meet the energy requirements for creating fine aerosols. Thus the mechanism of many accidental laboratory infections is clear.

Finally, with regard to the many infections that have a portal of entry somewhere in the upper respiratory tract, particle size of the aerosol is less crucial. In fact, larger particles, especially if they are moist or carry enzymes or toxic metabolic products, may be more infective than smaller particles. Such a mechanism might well be classed as true airborne infection, but this tends to approach droplet or contact infection and thus the two distinct modes of spread may become obscured.

In conclusion, I have endeavored in this review and interpretative analysis to trace the main events in the development of the modern concepts of airborne infection from the days of miasmas and malarias, when William Farr made the first steps toward applying the scientific method to then prevailing concepts, up to the present time when it is possible to marshal substantial and definitive epidemiological evidence supported by a large and growing body of experimental data. From this new evidence a sound Theory of Airborne Infection is developing. We can look to the future with a more scientific basis for discriminating good ideas from erroneous ones, and we can begin to outline appropriate control measures with the sense of purpose and effectiveness.

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