STUDIES ON THE COMMON COLD

V. THE RELATIONSHIP OF PATHOGENIC BACTERIA TO UPPER RESPIRATORY DISEASE IN INFANTS

BY YALE KNEELAND, JR., M.D., AND CAROLINE F. DAWES

(From the Department of Medicine of the College of Physicians and Surgeons of Columbia University, and the Presbyterian Hospital, New York)

(Received for publication, January 28, 1932)

It has long been known that pathogenic bacteria occur in the nose and throat of human beings with or without respiratory disease. Certain investigators (1, 2) who have followed individuals bacteriologically throughout the winter months have concluded that these organisms during colds probably play a part as late or secondary invaders. In certain unusual outbreaks of the common cold a specific bacterium has occasionally been so prominently associated with the disease as to suggest a primary etiological rôle. However, under conditions of ordinary civilized life it is difficult to evaluate the part played by bacteria in colds except in cases of frank purulent sinusitis or involvement of the deeper respiratory tract. Doehez, Shibley and Mills (3) observed that there was present in the nasal secretions of individuals suffering from early acute colds a filter-passing agent which was capable of giving rise to a typical acute cold when introduced into the nasal passages of a susceptible anthropoid ape or human being. They also noted that when they inoculated apes with this cold virus there was an immediate springing into prominence of certain pathogenic organisms in the nose previously occasionally present or not recoverable at all by culture. They suggested that the virus might produce severe symptoms by activating pathogens latent in the upper respiratory tract. This observation, however, cannot be exactly duplicated in human beings.

Bloomfield (4) in 1922 noted that the upper respiratory tract was sterile at birth, and commented on the rapid adaptation of green streptococcus to it. One of us (5) studied the bacteriology of the nose
and throat in infants during the first year of life. The tract was found to be sterile at birth, and to acquire immediately thereafter a flora comparable to that of adults except that the potential pathogens were absent. We observed that pathogens tended to appear at 2 to 3 months, but did not necessarily give rise to symptoms, and by 8 months the infant had a basal flora entirely comparable to that of adults. We noted that the first colds of infancy were mild, and showed no alteration in the normal bacteriology. Only in recurrent severe colds in slightly older infants, clinically suggestive of sinusitis, did it seem possible to implicate the pathogenic bacteria.

The factors affecting the incidence and spread of these organisms, their relationship to the character of the respiratory infections encountered, were deemed of sufficient interest to warrant a further clinical and bacteriological study in a semiisolated infant population.

**Methods**

The present observations were carried out from October, 1929, until July, 1931, at the Home for Hebrew Infants in New York City. We are indebted to Dr. Alfred F. Hess, its medical director, and the other staff members, whose interest and cooperation made the work possible. The Home is an institution giving permanent care from infancy to about 3 years of age to an infant population of approximately 300. Since visiting is permitted once a week, the community is only partially isolated from the outside world. Furthermore, as nurses shift from ward to ward at intervals, there is no strict internal isolation. New admissions to the Home are individually quarantined for 3 weeks, and then distributed to wards accommodating about twenty-five babies each. These wards contain babies of approximately the same age, and each infant progresses from bassinet to crib ward, then to high chair wards, and finally as toddlers to the grounds and playrooms. It is obvious that the opportunity for the dissemination of bacteria increases with age. The general hygiene and surroundings for all age groups are ideal.

During the 1st year of study, a group of ten infants was followed at weekly intervals. The 2nd year fifty infants were chosen, and studied at intervals of 2 weeks. All clinical observations were made by us personally, and it is probable that in the 2nd year a certain number of mild colds occurring in individual children between visits must have passed unnoticed. As the groups were visited in rotation, however, the factor of error must have been constant throughout, and may thus be minimized. As soon as a child had fever, it was transferred to the infirmary, and thus the census of the severer infections—grouped under the heading "grippe and pneumonia" on Chart 1—is accurate.

Cultures of the nares and oropharynx were made with a fine swab and imme-
YALE KNEELAND, JR., AND CAROLINE F. DAWES

Diately rubbed on freshly poured 5 per cent rabbit's blood agar plates. Plates were streaked out on returning to the laboratory, and read at the end of 20 hours' incubation at 38°C. Identification of the organisms was made by colony formation, morphology, and staining. Streptococci were tested for hemolysis in blood broth culture. All pneumococci were set up in Types I, II, and III sera, tested for bile solubility and injected into mice, those strains in which 0.2 cc. of a 20 hour blood broth culture was lethal being considered virulent.

Skin tests were performed monthly during the 1st year, and four times during the 2nd year. The antigens employed were derived as follows: for pneumococcus, a strain isolated from an adult case of sinusitis, which killed a mouse in dilution of 1:1,000,000 and was not agglutinated by the three typing sera, was grown for 22 hours in 100 cc. of 2 per cent proteose peptone broth. The sediment after centrifugalization was frozen and thawed twenty-four times, taken up in 100 cc. saline and filtered through a Berkefeld W. The filtrate, usually diluted 1:100, was used as the pneumococcus antigen. For H. influenzae, a stock strain, isolated from the epidemic of January, 1929, was employed. A filtrate from a 24 hour chocolate broth culture, diluted 1:100 was used. A strain of moderately hemolytic streptococci, also isolated from an adult's cold, was grown 72 hours on plain broth. The filtrate from this, diluted 1:10, constituted the third antigen. For skin testing, 0.05 cc. of each antigen was injected intradermally in the forearm. An area of redness about 1.0 cm. in diameter at the end of 24 hours was considered a mild but definitely positive reaction.

1. Results of Clinical and Bacteriological Study

Because the group studied during the 1st year was so small, the observations will not be reported in great detail, but the behavior of the pathogenic organisms in relation to respiratory disease will be briefly noted. Previous experience (5) had convinced us of the importance of pneumococcus and also of H. influenzae when the latter was present in large numbers in the nasal cultures. A light carrier state of H. influenzae in the throat was disregarded, as it was so extremely common. Hemolytic streptococcus was also considered. No other organisms comprising the basal flora were thought to be of significance. At the beginning of the observation period, the carrier rate of pathogenic organisms was very low; during November pneumococcus was recovered only once, hemolytic streptococcus not at all. H. influenzae was prominent in the nose in only one infant. The carrier rate for hemolytic streptococcus and Pfeiffer's bacillus approximately doubled in December, and fell again in January and February. During this period no disease was noted in the group studied. In March
the rate for *H. influenzae* abruptly shot up to 80 per cent, exactly coinciding with an outbreak of unusually severe respiratory infections throughout the Home, which included six of the infants under observation. These six infants survived, but there were several deaths although not among the group under observation, and we had the opportunity of culturing the lungs of two cases at autopsy. In one *H. influenzae* was the predominating organism. In the other, it was not recovered, the infection apparently being due to hemolytic streptococcus and *Staphylococcus aureus*. After the March outbreak the carrier rate of *H. influenzae* fell sharply to less than 50 per cent, the hemolytic streptococcus rising in April to the same height that Pfeiffer's bacillus had obtained the month before, associated with a less severe outbreak of infections. Following this there was a rapid decline in the carrier rate of these organisms, and by July the base-line had again been reached. After April all of the group studied were well. Throughout the winter pneumococcus behaved in a rather inconspicuous fashion.

During the winter of 1929–30, then, we observed that there was a sudden rise in the carrier rate for *H. influenzae*; this rise coincided with an explosive outbreak of severe respiratory infections; in one of two postmortem cultures the organism was isolated in large numbers from the lung. It would seem justifiable to conclude, therefore, that the very widespread dissemination of *H. influenzae* which occurred in March was related to the production of the epidemic described.

The character of events during the next winter (1930–31) is graphically shown on Chart 1. This chart embodies the clinical and bacteriological findings in a group of fifty infants. In the upper half is shown the carrier rate for the three pathogenic organisms. Pneumococcus present in the nose or throat is indicated by the solid line, hemolytic streptococcus by the broken line. *H. influenzae*, only recorded when prominent in the nose cultures, is shown by the dotted line. "Pneumococcus" here indicates all pneumococci, whether virulent or not. The virulent forms bore a fairly constant relation to the avirulent ones throughout the year, being roughly half of all those recovered. In the lower section of the chart the percentage of infants having respiratory disease each month is shown. Here the broken line indicates colds,
while the solid line represents all the infections associated with fever, whatever portion of the respiratory tract was involved. It will be noted that during the month of October the carrier rate for all the pathogens was extremely low, and that no severe infections were observed. However, there was already beginning a mild outbreak of colds, which reached its peak in November. Following the appearance of colds, there began a rise in the carrier rate of the three pathogens, and simultaneously a mild outbreak of the more severe infections.

**Chart 1.** The carrier rate for three pathogenic organisms of the upper respiratory tract is shown in relation to the incidence of colds and severe infections in a semi-isolated infant population.
infections. The latter reached its peak in December; as will be seen, the declining "cold" line is crossed by the "grippe and pneumonia" line. This coincides with the first peak in the carrier rate lines. At this time the most prominent organisms were H. influenzae and hemolytic streptococcus, with pneumococcus lagging behind, being found about half as frequently. During January and February the incidence of both colds and the severer infections fell off, associated with a decline in the carrier rate of hemolytic streptococcus and H. influenzae, both of which remained relatively low during the winter months. The pneumococcus, however, began to rise steeply, until it reached a high peak in March, at which time it was noted in 80 per cent of the group. This peak exactly corresponded with a marked outbreak of the severer respiratory infections, not associated with any antecedent rise in colds, thus duplicating the experience of the influenza bacillus the preceding year. There was one striking difference between the two epidemics, however; the cases just described associated with pneumococcus were considerably less severe than those related to the influenza bacillus the year before, and no deaths occurred. It will next be observed that as the "grippe and pneumonia" curve dropped off rapidly during the ensuing 2 months, there was a corresponding rise in colds, the June peak being associated with a secondary peak in the pneumococcus carrier rate. The pneumococci, with one exception, a Type III, always failed to agglutinate in the three typing sera.

DISCUSSION

We believe that the observations here recorded throw a certain amount of light on the pathogenesis of respiratory disease. In two successive years we have noted a rise in the carrier rate of a single pathogen taking place in the winter months in a semisolated infant population. In each instance a sharp peak was reached in the month of March, which corresponded with a similar peak in the incidence of severe respiratory infections. One year the pathogenic organism was H. influenzae; the next it was pneumococcus. The former was associated with much more severe infections. It seems reasonable to assume, therefore, that the very widespread dissemination of an organism such as the two observed by us is responsible for the severe
infections occurring in the midwinter. When the more elaborate study was made the 2nd year, however, more insight into the mechanism was forthcoming. As one observes the sequence of events recorded in Chart 1, one sees no alteration in the group bacteriology accompanying the first colds of autumn, nor are there any associated severe infections. One can assume, therefore, that these disturbances are due to the virus of the common cold. There follows an increase in the carrier rate of the pathogens; we may assume that the cold virus has made the soil more favorable for the dissemination of these bacteria, as has been experimentally shown to occur in the anthropoid ape. Then a few severer infections begin to appear, with the incidence of colds dropping off. As autumn changes into winter, the pathogenic organism spreads, until 80 per cent of the infants harbor it. Exactly at the time when this widespread carrier state of pneumococcus exists, another wave of respiratory disease supervenes, but now instead of manifesting itself as the common cold, it takes the form of more serious infection, grippe and pneumonia. Over 40 per cent of the group under observation were admitted to the infirmary because of respiratory disease during the month of March, but there was no significant rise in colds.

The age of the infants has a definite relationship to susceptibility to infection. Barenberg, Greene and Abramson (6) reported that institutional children were more susceptible to pneumonia between the ages of 6 months and 2 years, and that the case rate for those less than 6 months of age was very low. During the 2 year period we also have observed that infants in the first few months of life are comparatively immune. Children more than 18 months of age have numerous colds, particularly chronic colds, but are only moderately susceptible to grippe and pneumonia. Infants between 8 and 14 months of age, however, are highly susceptible to serious respiratory disease, and most of the pneumonias occur in this group. There were 21 infants of this susceptible age group under observation in March, 1931. During this month the carrier rate for pneumococcus was 95 per cent, and 53 per cent of the group had grippe or pneumonia. At the same time only 5 per cent had the common cold. In other words, the relationship between colds and the severer infections was strikingly reciprocal in this group. Chart 2 shows this behavior and compares it with that of
the older children, those known to be less susceptible to serious respiratory disease, who had a very high incidence of the common cold—40 per cent. It seems, then, that in the susceptible group

![Chart](image)

**Chart 2.** The behavior of the highly susceptible infants between 8 and 14 months of age is contrasted with that of older children during the March epidemic. The former group showed a very low incidence of colds and a very high incidence of severer infections. Coincidentally the latter group showed an equal incidence of both types of infection.

those destined to have respiratory disease had not the common cold, but a deeper, more serious infection. It is possible, therefore, that the March outbreak of grippe and pneumonia, like the autumn wave of colds, is initiated by the cold virus, but in this case it is cold virus
acting in conjunction with an almost universal carrier state of a pathogenic organism in late winter.

2. Results of the Skin Tests

Positive skin reactions were not obtained in very young infants, and only rarely before 6 months of age. They were more frequently encountered in children over 1 year of age than in the other age groups. In the autumn the percentage of those showing positive reactions to one or more of the antigens was low, about 30 per cent, and it continued to decline until December. It then rose rapidly until spring, when it reached about 80 per cent, and fell off during the summer. In general, the best antigen was that derived from H. influenzae; by far the poorest was the pneumococcus. Positive reactions to the latter were very seldom observed, and, as far as could be told, were without particular significance.

The skin tests were undertaken with a view to determining whether susceptibility to respiratory disease could be correlated with the development of hypersensitivity in the skin to the secondary invaders. This could not be shown with the three above described antigens as employed. In only one infant could a definite correlation be made between the characteristic flora of the respiratory tract and skin sensitivity. This infant was the only steady carrier of hemolytic streptococci in the group, and over the 2 year period he gradually developed a violent delayed reaction to the streptococcus filtrate. This was by far the most strongly positive skin reaction that we observed, but was not associated with any increased susceptibility to respiratory disease.

As far as we could determine, the seasonal alteration in skin sensitivity was probably a reflection of the respiratory history of the institution. The steady winter rise in skin reactivity reaching a point in the late spring where four-fifths of the infants were positive to one or more antigens, the decline in reactivity during the summer and autumn, seemed to be a sequel to the seasonal flow and ebb of respiratory disease, and without significance in any individual case.

CONCLUSIONS

1. Bacteriological and clinical observations on respiratory disease in a semiisolated infant population over a period of 2 years are recorded.
2. In two severe winter outbreaks of respiratory infection a parallel rise in the carrier rate of pathogenic organisms was noted.
3. The first autumn outbreak of colds seems to favor the dissemination of the pathogenic organisms.
4. The relationship of colds to the severer infections is roughly reciprocal.
5. Infants between 8 and 14 months of age are subject to the most severe infections.
6. The number of infants showing positive skin reactions to products of pathogenic organisms increases during the winter months.
7. The significance of these findings is discussed.

BIBLIOGRAPHY