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The Replete Pediatrician and the Etiology of Lower Respiratory Tract Infections

Presidential Address to the Society for Pediatric Research[1]

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In opening this address I want to express to the members of the Society for Pediatric Research my deep appreciation for the honor conferred upon me by making me their president. As demonstrated during the business meeting, there has been some unrest regarding the activities of this Society during the past year. Along with most things today, pediatric research is in a state of great flux, with good and bad things taking place. With this state of affairs, it seemed prudent for our Society to make changes in accord with the will of its membership. I believe your Officers and Council have responded to your desires; I hope so. Possibly because of some of our problems, I have developed a new and greater appreciation of what this Society means to pediatrics and to pediatric research and I have enjoyed being an intimate part of it. I thank you for making this possible.

On learning that I would be in this position, one of my first thoughts was what I should include in this address, a situation that I understand has been shared by most if not all of those who have walked this path ahead of me. Since this is the Society for Pediatric Research and since all of my research has dealt with infections of the respiratory tract, it seemed only natural and appropriate that I should choose a topic in this area. I did not think that I would need to justify discussion of some aspect of this subject, because infections of the respiratory tract are the most common infections suffered by man. My further thinking was colored greatly by the increasing emphasis in academic medicine to move out of the university and its affiliated hospital into the community, and the increasing need to apply knowledge gained in the research laboratory to the care of patients. With these things in mind, I was led eventually to the decision to talk about infections of the lower respiratory tract in nonhospitalized children in an open community and how the observations made in such studies could help answer questions raised by the clinician as well as the investigator.

It has been demonstrated that all classes of microorganisms known today can infect the respiratory tract of man. Rickettsial, fungal, protozoal, and parasitic infections, as well as tuberculosis, are beyond the scope of this presentation. Bacteria are common and important causes of respiratory tract infections. I give as examples the group A streptococcus as a cause of pharyngitis and the pneumococcus and *Hemophilus influenzae* as causes of otitis media and pneumonia. Most investigators agree, however, that the majority of infections of the respiratory tract are not caused by bacteria; this is particularly true of infections of the lower respiratory tract. Unfortunately, the overall role of bacteria as causes of lower respiratory tract infections is not well understood and has proved very hard to study. The greatest problem encountered in trying to answer this question is that, in most instances, material for culture cannot be gotten safely from the involved tissue. Cultures can be obtained from the upper respiratory tract, but it has been difficult to relate bacteria isolated there to disease processes of the lung and trachea. This is primarily because a high percentage of normal children of all ages harbor bacteria in their upper respiratory tracts in the absence of any disease. In addition, serological methods that would help to relate most bacteria to disease are either unavailable, unreliable, or so tedious that they are not applicable to routine laboratory use. The sad state of the art is further emphasized by the unavailability of many fast and reliable office diagnostic procedures and the failure to develop any reliable and effective respiratory bacterial vaccines since diphtheria and pertussis. Because of the difficulties we and others have had in studying bacteria in the respiratory tract, I shall not discuss them further. In so doing I can only urge that more attention be given by more investigators to these important causes of childhood disease.

This leaves for discussion the respiratory viruses and the one mycoplasma species that has been demonstrated to be pathogenic for man, *Mycoplasma pneumoniae.* Studies with these agents have been greatly facilitated because they cannot be isolated from most normal children, and it has been demonstrated repeatedly that their isolation from the nasopharynx and pharynx can be related reliably to disease processes in the lower respiratory tract. Viruses and *Mycoplasma pneumoniae* have been shown to be the most common causes of respiratory infections for which the etiology has been determined. Although the cause of a sizeable group of respiratory infections has not been identified, it seems probable that yet unidentified viruses or mycoplasmas will be found to be important. In spite of the obvious significance of this group of agents, not enough is known about their relation to illness or how the practicing physician can diagnose, treat, or prevent diseases they cause. Rapid means of diagnosis are either lacking or are in the experimental stage, leaving the pediatrician to his clinical devices to determine the causative agent and, with this, the decision of whether or not to treat with antibiotics. Although much effort is being put into the development of vaccines to several respiratory viruses and to *Mycoplasma pneumoniae,* up to the present time many obstacles have been encountered and, with the exception of influenza virus vaccine, no products have been licensed for general use.

Because, of the importance of this problem and because we have been working in this area, I want to share with you some of our current thoughts. From studies of respiratory infections in ambulatory patients, we have developed a few concepts that we think might be of help to the pediatrician in making more accurate etiological diagnoses. Some of the observations that have been made are pertinent to the development, use, and evaluation of vaccines and may be helpful in clarifying some mechanisms of pathogenesis. Buffs of growth and development will also see the relevance of some of these studies to their area of interest.

The work to be reported was done in children who were patients of three pediatricians in a partnership practice in Chapel Hill, North Carolina. All children with lower respiratory tract disease, who were ill enough to be brought to these pediatricians, were admitted to a special study. After an appropriate history was taken and a physical examination was performed, the major site of disease within the respiratory tract was determined. For these studies, the lower respiratory tract was defined as the epiglottis or below and was arbitrarily divided into the larynx, the trachea and bronchi, the bronchioles and the alveoli. Or to put it into terms of disease, the patients were diagnosed as having croup, tracheobronchitis, bronchiolitis, or pneumonia. Cultures were then taken from the upper respiratory tract and transported promptly to our research laboratory. Here they were processed by conventional techniques, and viruses and *Mycoplasma pneumoniae* were identified by appropriate methods.

Table I. Common nonbacterial agents found in children with lower respiratory illnesses

Respiratory syncytial virus
Parainfluenza virus type 1
Parainfluenza virus type 3
Mycoplasma pneumoniae

Table I lists the agents that are going to receive further attention this morning. In studies done by us and in other laboratories, these agents are the most common and important causes of respiratory disease in children. Furthermore, they are responsible for a large part of the respiratory infections for which etiological agents have been discovered. This is not to indicate that other agents are not important, but they were isolated less frequently and our observations are less complete than with the above organisms. The adenoviruses, influenza viruses, rhinoviruses, and Coxsackie viruses continue to receive our attention and evaluation. Other viruses, which can be isolated from the respiratory tract, such as the agents causing rubella and mumps, are omitted because they are associated with more extensive disease in other parts of the body and in this respect are not true respiratory viruses.

In subsequent figures, it will be shown that these four agents have distinct tendencies to occur in epidemics or at a particular time of year, to infect children of a specific age, and to involve rather selectively one part of the respiratory tract more than another. Observations of this type have been made by astute clinicians for many years, but only recently have techniques been available for adequate identification of agents and the painting of a clearer picture. I want to emphasize the importance of making these observations in nonhospitalized children. Most studies reported up to this time have been done in children ill enough to be in the hospital. While this may be a good measure of severe illness, it has been demonstrated that it is a poor measure by most other criteria.

Figure 1 shows the periodicity of common nonbacterial agents from children with lower respiratory tract illnesses during a five-year period from 1964 through 1968. Four distinct patterns of isolation of the agents were observed. The respiratory syncytial virus occurred in winter or in late winter and spring outbreaks during each year of the study. These outbreaks were of interest to us because, as demonstrated in 1964 and 1965, a late winter and spring outbreak one year was followed the next year by an early winter outbreak. This is a pattern that has recurred up to the present time. The important point, however, is that this agent has appeared every respiratory disease season in which it has been studied.

The isolation of parainfluenza virus type 1 has followed an entirely different pattern. This agent has caused epidemics that begin in the summer and extend into the fall and early winter and, so far, have occurred every other year. During the intervening years, this organism has not been isolated from our populations.

Parainfluenza virus type 3 has a third and distinct type of occurrence in that, with the exception of a few months, it has been possible to isolate this agent with regularity during the entire study period. There have been two mild epidemic peaks but, in general, this organism has not caused sharp outbreaks as frequently as have the respiratory syncytial virus or parainfluenza virus type 1.

Still another pattern of occurrence of infection was seen with *Mycoplasma pneumoniae*. Two prolonged and smoldering epidemics have occurred. Each of these lasted for many months and without particular relation to season. During the intervening months between epidemics, it has not been possible to isolate the agent from patients in our community.

The periodicity of these four agents has been so distinctive that we are watching with great interest what happens each year in our population groups and in other parts of the country or in other countries throughout the world. It is already apparent that the patterns of disease that I have described are not always identical in all parts of this country every year. The very distinctive patterns that have occurred, however, point very strongly to the continued need of such observations.

The frequency of the four agents by age of children with lower respiratory tract illnesses is shown in fig. 2. The patterns with respiratory syncytial virus and parainfluenza type virus type 3 were very similar. Infections with these two organisms began to occur in the first few months of life, produced significant amounts of disease during the first few years of life, and then declined rapidly in frequency so that infections were unusual after entry into school. The frequency of infection with parainfluenza virus type 1 showed distinct differences. Infection with this agent was unusual during the first six months of life and reached its peak during the second six months. It also tended to cause disease more frequently in the school age child, although this was not a striking finding. The pattern for *Mycoplasma pneumoniae* was sharply different from that of the other three agents. Infection was unusual before entry into school and reached its peak during the early teen-age years. If data such as these can be reproduced over a greater number of years and in widespread areas, their significance will increase markedly.

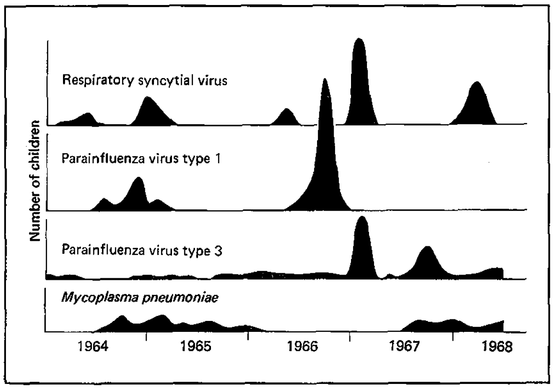

Fig. 1. Periodicity of common nonbacterial agents from children with lower respiratory tract illnesses.

Figure 3 shows the association of these agents with involvement of different parts of the lower respiratory tract. I should point out that the figure is very diagrammatic and I have taken some statistical license in its preparation. I justified the use of the flowing line graph because I am sure that it is as accurate as is the attempt to separate clearly involvement of the different parts of the respiratory tract. The first thing that this figure demonstrates is that all of these agents can infect all parts of the respiratory tract, and the propensity to involve one part of the respiratory tract more than another is only relative. There are, however, certain trends that seem worthy of consideration. The most striking association is between parainfluenza virus type 1 and involvement of the larynx. This agent was the most common cause of croup but infrequently involved the other lower respiratory structures. Respiratory syncytial virus had a slight tendency to associate with more disease in the lowest parts of the respiratory tract, while just the opposite seemed to be true with parainfluenza virus type 3. Although quantitatively a smaller problem, the trends with *Mycoplasma pneumoniae* were quite sharp in that this organism was more frequently associated with pneumonia than with croup. The data presented here were derived from the entire group of patients and, for simplicity, have not been broken down by age or time period. When this is done, the propensity for an agent to affect a certain part of the respiratory tract becomes more impressive.

These studies have depicted clearly the importance of consideration of the time of infection, the age of the patient when infected, and the location of the infection within the respiratory tract. These trends have been consistent from year to year, and an accurate overall picture of the disease caused by certain agents is de-

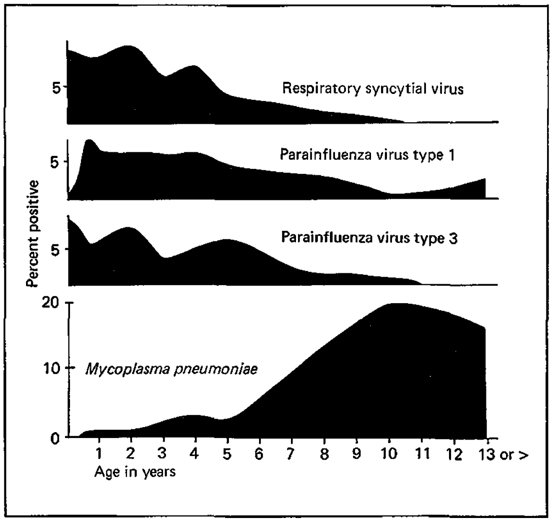

Fig. 2. Frequency of agents by age of children with lower respiratory tract illnesses, 1964–1968.

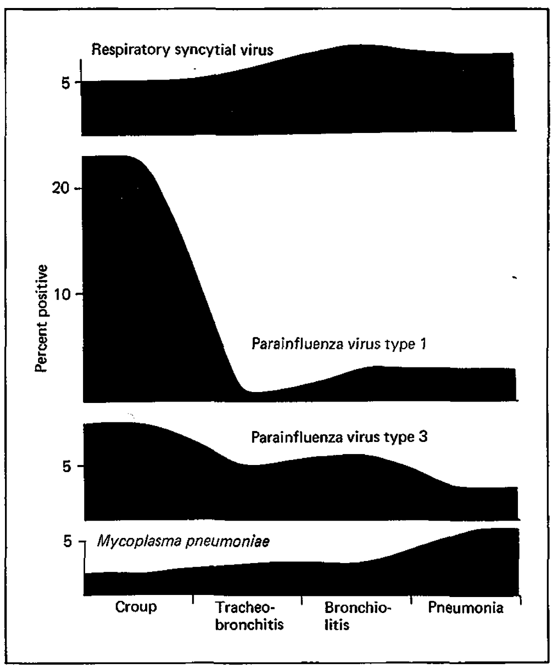

Fig. 3. Association of common nonbacterial agents with lower respiratory tract illnesses in children, 1964–1968.

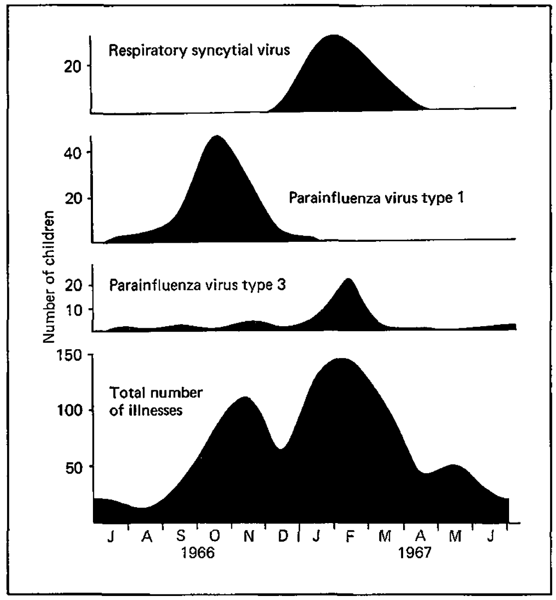

Fig. 4. Common nonbacterial agents from children with lower respiratory tract illnesses by month.

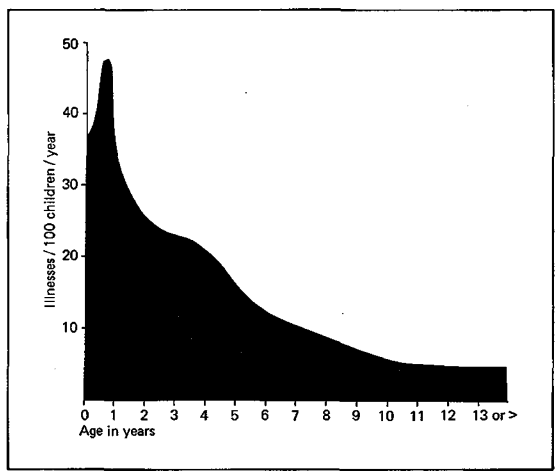

Fig. 5. Frequency of lower respiratory tract illnesses by age, 1966–1967.

veloping. It is not possible, however, from the data presented to determine the risk of infection to all children in the community and, for that reason, the actual size of the problem under study. With this in mind, all patients enrolled in the pediatric practice for one respiratory disease season, 1966–1967, were tabulated by age. This gave a reasonably accurate denominator from which rates could be calculated for the various facets under study. The following figures depict this part of our investigations.

Figure 4 shows the occurrence of the common nonbacterial agents in children with lower respiratory tract illnesses by month for the respiratory disease season 1966–1967 and is a reproduction of the last part of fig. 1. Almost 800 lower respiratory tract illnesses were observed and, as shown in the lowest frame, these occurred in a double-humped epidemic during the winter and spring months. The most common organisms isolated were the respiratory syncytial virus, parainfluenza virus type 1, and parainfluenza virus type 3. The periodicity of infection with these agents is well demonstrated. It is of interest that *Mycoplasma pneumoniae* was not present in our community at this time and therefore cannot be included in these observations.

Using the numbers of children enrolled in the practice as a denominator, it was possible to determine the rates of occurrence of lower respiratory tract illnesses by age, as is shown fig. 5. The remarkable frequency with which the lower respiratory tract can be involved in very small children is demonstrated; almost 50 illnesses per 100 children were observed during the first year of life. The frequency of infection decreased rapidly so that by the age of 10–12 years it was only about one tenth of what it had been earlier.

These figures can be broken down still further by the site of primary involvement of the lower respiratory tract; this information is depicted in fig. 6. Croup occurred infrequently during the first few months of life, reached its peak during the second six months, and then declined rather sharply and occurred infrequently after the age of entry into school. Tracheobronchitis occurred most frequently in the first few years of life, but there was significant occurrence throughout the age groups under observation. The occurrence of bronchiolitis during the first few months of life is demonstrated graphically. Pneumonia also tended to occur more frequently in the very young but remained a problem in all age groups. The peak at four years of age is not explained.

Further information regarding differences according to age are shown in fig. 7 where the frequency of agents by age of children with lower respiratory tract illnesses is shown. The great frequency with which respiratory syncytial virus and parainfluenza virus type 3 are found in the first few months and first few years is clearly demonstrated. The relative infrequency of parainfluenza virus type 1 in the first few months of life, the peak occurrence in the second six months, and the gradual decline thereafter are also apparent. The similarity between the curves for croup shown in fig. 6 and parainfluenza virus type 1 shown in this figure are obvious. The correlations between specific agents and the site of infection in this segment of the study are similar to those shown for the entire group. As with the larger group, other correlations could be made but those presented are representative of the points I want to make. Furthermore, the data have shown that the agents under study cause a large amount of significant respiratory disease in normal population groups and are deserving of serious consideration on our part as physicians and investigators.

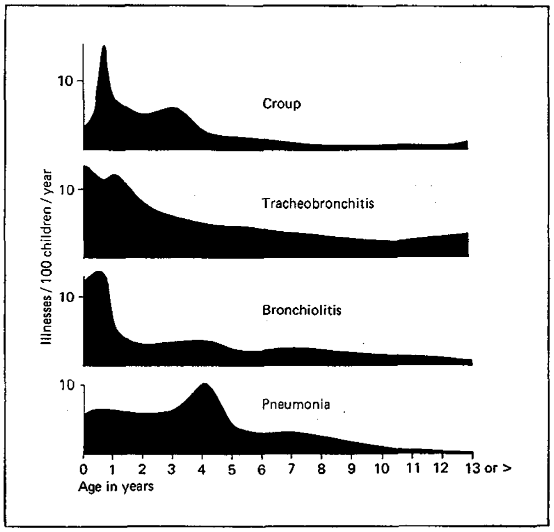

Fig. 6. Frequency of lower respiratory tract illnesses by age, 1966–1967.

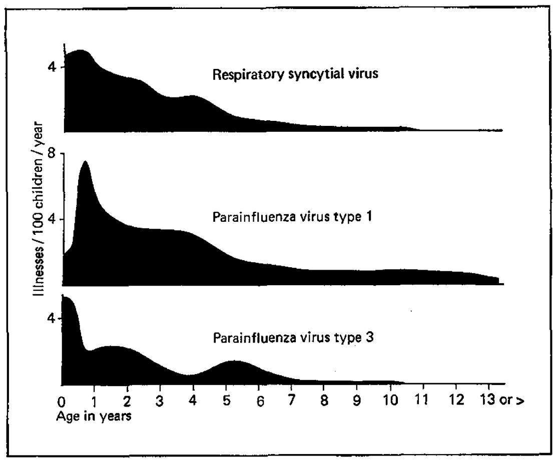

Fig. 7. Frequency of agents by age of children with lower respiratory tract illnesses, 1966–1967.

To demonstrate that these observations are not restricted to infections of the lower respiratory tract, I should like to show you that at least some of the same things apply to involvement of the upper respiratory tract. During the year 1964–1965, a study was made in this same practice of pediatrics of 750 children who presented themselves to the physician with an illness that was diagnosed as pharyngitis. The children were studied for the presence of viruses, group A streptococci, and *Mycoplasma pneumoniae*. These patients were

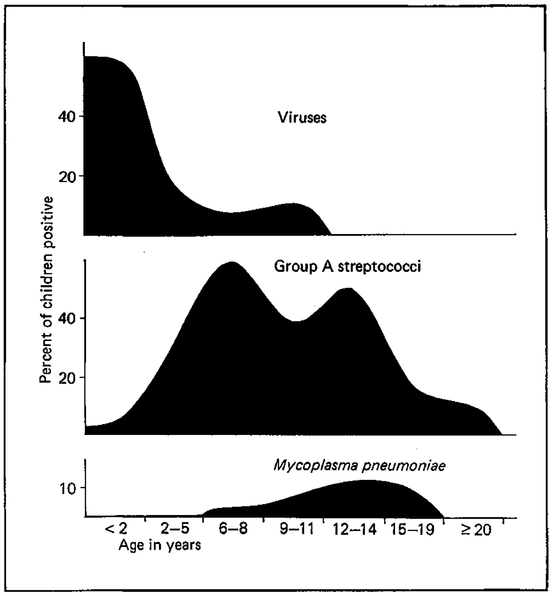

Fig. 8. Frequency of agents by age of children with pharyngitis, 1964–1965.

Table II

Diagnosis with appropriate treatment
Development of preventive measures
Study of pathogenesis
Personal satisfaction

picked because of the site of their infection and the periodicity of the occurrence of at least some of the agents found has already been adequately shown. The frequency of these agents by age of the children is depicted in fig. 8. The great tendency for viruses to cause pharyngitis during the first two or three years of life, the group A streptococcus to infect young school age children, and *Mycoplasma pneumoniae* to cause infection in the teen-ager are all demonstrated.

At the beginning of this address I mentioned several reasons why studies of the type I have presented could be of importance. These are listed in table II. In 1969, the generally accepted way to make a diagnosis of an infectious disease is to isolate the agent or demonstrate the appearance of specific antibody in the patient's blood. Such techniques applied to nonbacterial agents are time consuming, tedious, and expensive, and because of these, cannot play a prominent role in the immediate diagnosis and treatment of most patients. Investigations in several laboratories are being directed towards making diagnoses more rapidly with such techniques as fluorescent antibody staining of exfoliated cells. These techniques are not ready for wide usage, however, and it is doubtful that they will ever play a role in the office diagnosis of respiratory disease. Clinical and epidemiological tools of the type shown remain then the only methods for the practicing physician to use. Consideration of the age of the patient, the time of the infection, and the site of the infection within the respiratory tract, if properly interpreted, can be extremely helpful in arriving at a diagnosis with determination of subsequent treatment. Care should be exerted, as with any other tools in medicine, not to over-interpret the data and by so doing deprive a patient of appropriate therapy.

I should like to speculate for a moment how I visualize the pediatrician using these methods. Knowledge of the prevalent microorganism in a community or section of the country is essential and should be supplied by regional or district laboratories. This information, along with pertinent historical and clinical data supplied by the pediatrician, could then be studied statistically, possibly by an office computer, and a diagnosis derived. I should guess that a diagnosis reached by this procedure would be considerably more accurate than most of our clinical opinions. In any event, this approach seems worthy of evaluation.

Antimicrobials effective against the viruses discussed are not available. Tetracycline and erythromycin are moderately affective in shortening the course of *Mycoplasma pneumoniae* disease but do not eradicate the organism. For these reasons it seems highly desirable to explore, and develop if possible, some types of preventive measures. The development of vaccines against all of the agents discussed is in progress but, up to now, the problems encountered have been immense and the progress slow. Data such as those presented are essential as a baseline or background for the development of vaccines. They show the relative roles of the agents as causes of disease in a community and suggest strongly the age group of children in which vaccines should be used and evaluated. For instance, it would appear that it would not be necessary to use a vaccine against *Mycoplasma pneumoniae* until a child is ready to start to school. On the other hand, vaccines against the respiratory syncytial virus and parainfluenza virus type 3 must be given in the first few weeks of life if the greatest amount of disease is to be prevented.

Probably the most interesting aspect of studies such as these is some suggestion for clarification of the pathogenesis of infection. Infection with *Mycoplasma pneumoniae* is a good example. Our studies have demonstrated, along with others, that significant illness does not occur during the first few years of life. In contrast, it has been shown by some investigators that the very young child becomes infected but does not have clinical illness. These observations, along with the demonstration that

Mycoplasma pneumoniae infection is associated with the formation of very curious immunoglobulins, lead one to speculate that the signs of illness may be mediated through some hypersensitivity state.

Another example is the frequent occurrence of respiratory syncytial virus and parainfluenza virus type 3 disease in the first few months of life. This occurs in spite of the presence in all newborns in this country of high-titered antibody that is acquired passively from mothers who universally have had natural infection. This is in contrast to the relative infrequency of parainfluenza virus type 1 infection in the first few months of life, when it would appear that circulating antibodies might be effective. Furthermore, it has been demonstrated that respiratory syncytial virus disease during the first few months after birth is a much more severe disease than later in life. This, and the demonstration that infants receiving killed-virus vaccine with the subsequent development of circulating antibody have more severe disease than do uninoculated controls, suggest that the illness might be mediated through some antigen-antibody mechanism. These observations also suggest that local or secretory antibody might be necessary for adequate protection of the child.

The role of satisfaction to the practicing physician cannot be overemphasized. The fact that one is dealing with a known entity is always comforting, even though one may feel helpless in changing its course. It is refreshing also to see how much can be accomplished in educating young parents when good data are available to support the withholding of an antibiotic.

At the start of this address, I pointed out that one of the motivations for choosing the present topic was its relation to community pediatrics and to the practicing pediatrician. I hope it is obvious to you now, the relation of the studies presented to both of these. I can assure you that the results reported could not have been obtained from any group but an open and ambulatory population. The role played by the practicing pediatrician was a real one and, indeed, the studies could not have been done had they not been willing to be an integral part of our group. Furthermore, it has been an invaluable experience for me – one that I can recommend to all of you most heartily.

In closing this address, it would be remiss of me if I did not recognize certain people who have been instrumental in helping me along the way which has led to this podium. I am deeply grateful to my family for their support over the years. I am also indebted to the following: Dr. Amos Christie, who by his example led me into pediatrics; Dr. Charles Rammelkamp, who introduced me to the research laboratory; Dr. John Dingle, who has been my ideal and counselor; Dr. William Wallace, who has been my conscience in clinical and research problems; Dean Reece Berryhill, who has understood and supported me over the years; and finally, my co-workers in the laboratory and in the practice of pediatrics, who really did the work.

References and Notes

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2. This work was done under the sponsorship of the Commission on Acute Respiratory Diseases of the Armed Forces Epidemiological Board, and was supported in part by the U.S. Army Medical Research and Development Command, Department of the Army, under research contract No. DA 49-193-MD-2189 and was also supported in part by research contract No. PH 43-67-48, Vaccine Development Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health.
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