THE PROTECTION AFFORDED BY VACCINATION AGAINST SECONDARY INVADERS DURING COLDS IN INFANCY

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Studies of the mechanism of epidemic respiratory diseases in a concentrated infant population previously reported (1) have indicated that the etiology of these disorders may be a complex one. It has been noted that respiratory infection occurring in the autumn, when the carrier rate of pathogenic bacteria is low, usually takes the form of a minor disturbance of the type of the common cold. Later on, in the winter months, when a widespread dissemination of pathogenic bacteria takes place in certain groups of infants, an outbreak of infections in these groups takes on a more serious character. The majority of these infections present two features in common, fever and constitutional reaction; thus they are no longer designated as colds, but rather as grippe, pharyngitis, otitis media, bronchitis, or pneumonia, depending on the region principally involved. During the past few years it has been established that there exists in adults suffering from the common cold (2–5) a typical filtrable virus. There is every reason to suppose that this virus is equally pathogenic for infants. It has therefore been possible to construct an hypothesis as to the mechanism of development of epidemic respiratory diseases in infants: the filtrable virus alone produces the mild autumnal disturbance, the common cold; later on, when the carrier rate of pathogenic organisms becomes very high, it acts as an initiating agent which permits these bacteria to produce more severe infections.

Because of the existence of this filtrable virus, it is illogical to suppose that vaccination of adults with the bacteria of the upper respira-

1 These studies were made at The Home for Hebrew Infants in New York City through the courtesy of the late Dr. Alfred F. Hess and other members of the staff.
tory tract would prevent the common cold, and this has been amply established by most of the well controlled experiments along this line (6-9). On the other hand, if our hypothesis in regard to the etiology of epidemic respiratory diseases in a dense infant population be correct, vaccination with the secondary invaders should diminish the severity of the febrile and complicated forms of these diseases. A study, therefore, was conducted with this in view.

The only record that has been found of the use of such vaccines in early infancy is included in a report by Stoltenberg (10). New admissions to a children's hospital in Oslo were treated with a bacterial vaccine, and of a group of 500 so treated during a 5 year period, approximately 50 were under 1 year of age. A similar number of infants in the preceding 5 year period were considered as controls. The frequency of febrile infections was given as roughly five times greater in the non-vaccinated group, and the number of complications also larger.

Previous experience (1) had led us to the belief that pneumococcus, H. influenzae, and hemolytic streptococcus are the most important pathogenic bacteria of the upper respiratory tract in infancy. It was therefore decided to employ a vaccine composed only of these organisms, in the hope that its simplicity would render it a more effective antigen than the average "catarrhal" vaccine.

Methods

Pneumococci were cultivated for 24 hours in beef infusion broth. The washed organisms were taken up in salt solution with 0.2 per cent phenol and heated to 60°C. for 30 minutes. Because of the fact that a considerable variety of types is recovered from infants—and it seemed difficult at the time to include all of these—it was thought that the most one could hope to produce was a non-type-specific active immunity. Consequently, the Neufeld strain of Type I pneumococcus was employed. It has recently been shown, however, by Goodner and Stillman (11) that this non-type-specific immunity is low in rabbits when their resistance to dermal pneumococcus infection is quantitatively estimated.

The hemolytic streptococcus vaccine was similarly prepared, except that it was heat-killed at 60°C. for 1 hour. Four strains, supplied by Dr. M. H. Dawson, were employed, derived from scarlet fever, rheumatic fever, erysipelas, and rheumatoid arthritis respectively. Dr. Margaret Pittman of The Rockefeller Institute kindly provided us with two smooth strains of H. influenzae, Types A and B. These organisms were cultivated 24 hours in clear chocolate broth, washed, suspended in carbolized saline, and heated to 60°C. for 45 minutes.

A group of twenty-three infants at the Home was designated as the one for study, and a comparable group of twenty-three in identical surroundings as the...
control. The average age of each at the beginning of the observation period was 6.4 months. Starting in the latter part of October, 1932, a course of nine subcutaneous injections of the vaccine was administered to the first group. The initial dose of organisms was 45 million, the final dose 750 million. The proportion of pneumococcus to \textit{H. influenzae} to streptococcus in each mixture was 5:3:3 approximately. Early in February a second course of seven weekly injections was administered to the treated group. The initial dose in this course was 190 million, the final dose 1000 million.

Some local redness and induration were produced by the larger doses of vaccine. No febrile or constitutional reaction was ever observed. It is to be noted that the administration of vaccine was always omitted if the infant had a febrile respiratory infection at the time; in this way, three members of the vaccinated group missed nearly all of the second course. They were not excluded, however, on this account from the tabulation of the clinical history of the group.

\textbf{RESULTS}

The two groups showed no significant difference in the incidence of minor respiratory infection of the type of the common cold.

The experience of each group in regard to the febrile forms of respiratory disease is graphically indicated in Chart 1. In this chart is given the total number of days of temperature over 100° due to respiratory disease for each month in the two groups. It will be observed that there was very little febrile infection during October. In November, half way through the first course of vaccine, the two groups fared almost identically. In December, also, the difference was slight. By January, however, there was a striking difference between the vaccinated and the control, the latter showing three times as many days of fever as the former. The peak of respiratory disease was reached in February, and in this month—half way through the second course—it will be seen that the difference between the groups is less marked, for the vaccinated infants showed more than half as many febrile days as the controls. There is a falling off for both groups in March, but it is to be observed that while this decline continues in the vaccinated group during April, it does not do so in the control. In May, both fell to their original low level.

The actual number of individual respiratory infections of all types per child—5.4 in the vaccinated, and 5.8 in the control—was almost the same in the two groups. The difference in severity, however, is further illustrated by the incidence of pneumonia; there were five cases
among the controls as opposed to two in the vaccinated, and of the latter one case occurred when the first course of vaccination was only half completed.

In spite of the fact that the N. Y. 5 strain of scarlatinal streptococcus was included in the vaccine, two of the vaccinated children developed scarlet fever, as well as one control. There was evidence, however, that the causative streptococcus of this outbreak was an atypical one.

**DISCUSSION**

The data obtained in this experiment give evidence that vaccination of infants against certain bacteria of the upper respiratory tract...
modifies in degree the subsequent respiratory disease which these infants will undergo. There is no alteration in the number of acute infections, and no change in the simple catarrhal infections of the upper respiratory tract. There is, however, a significant alteration in the severity of respiratory infection, as measured by the number of days of fever that occur. The age group selected for study was the one in which our experience indicated that the greatest incidence and severity of respiratory infection might be expected during the winter months. Even in this age group which, in institutions, invariably shows so high a susceptibility to epidemic respiratory disease, vaccination with common pathogens is effective in reducing the severity of these epidemics. The interest here lies chiefly in such light as is thrown on the mechanism of epidemic respiratory disease. Earlier in this report an hypothesis was put forth that the character of certain winter outbreaks of grippe, etc., is determined by the presence of a widespread carrier state of ordinary pathogenic bacteria; the study herein described would seem to lend additional support to this hypothesis, inasmuch as vaccination with these pathogens has been found to modify significantly the severity of these outbreaks.

Certain other features of these results are worthy of brief comment. A study of the curve given in Chart 1 would seem to indicate that immunity in these infants did not manifest itself until a rather large amount of vaccine had been administered. It would also appear that the immunity finally engendered did not last much more than 2 months.

With the increasing data now available as to the frequency of the various newly identified types of pneumococcus carried in infancy, it seems probable that more striking results would have been obtained by the use of a vaccine containing these types instead of Type I.

**SUMMARY AND CONCLUSIONS**

An intensive course of vaccination with the pathogenic bacteria of the upper respiratory tract modified favorably the winter outbreak of severe respiratory disease in an infant population. The incidence of the common cold was not affected.

The significance of these findings is discussed.
VACCINATION OF INFANTS

BIBLIOGRAPHY

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