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The Antibody Responses to Pneumococcal Capsular Polysaccharides in Aged Individuals (40868)[1]

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Abstract. A population of elderly individuals was studied following immunization with the pneumococcal capsular polysaccharides of types 3 and 8. The antibody responses, determined by indirect hemagglutination (IHA) and by radioimmunoassay (RIA), before and 2 weeks following immunization were compared to those in young adults. Immunoglobulin levels were measured prior to immunization. The numbers of individuals showing a significant increase in antibodies to the polysaccharides of pneumococcal types 3 and 8 were comparable in both age groups when assayed by IHA and RIA. In addition, the mean fold increases in levels of antibodies measured by IHA and by RIA were not significantly lower to either polysaccharide in the elderly group. Postimmunization levels of antibody in the elderly, determined by RIA, were lower to both polysaccharides studied than in young adults, but only those to pneumococcal polysaccharide type 3 differed at a stastically significant level. Comparison of immunoglobulin levels in elderly responders and nonresponders suggested an association between low values of serum IgM and IgA and lack of responsiveness to immunization with pneumococcal polysaccharides.

The involution of the immune system in man and in animals has been the subject of numerous studies in the past decade. Evaluations of T- and of B-cell function have shown, in general, abnormalities of both T- and B-cell functions, although the reported studies do not always agree as to the specific functions which are altered. In the aged mouse, increased formation of autoantibodies (1, 2, 3), abnormalities in antibody responses (4, 5), and decreased suppressor cell activity (6) have been described. In aged humans, similar abnormalities have been reported including decreased levels of IgM, increased levels of IgA (7, 8, 9), increased autoantibody formation (10, 11), and depressed T-cell function as assayed by skin tests of delayed hypersensitivity (12, 13). Studies of T-cell formation, as assayed by mitogen stimulation, and of suppressor cell function have not shown consistent results (13).

Because the susceptibility to fatal infection with *Streptococcus pneumoniae* in adults increases with age (14), we have sought to determine the antibody response of a population of 66 elderly individuals to antigens of purified pneumococcal capsular polysaccharides. Although a previous study had demonstrated normal responses in elderly individuals (15), the ages of the individuals were not given. In this study, individuals ranged in age from 57 to 100 years (mean age 78 years).

Materials and methods. Patients and controls were immunized subcutaneously with monovalent preparations of purified PPS types 3 and 8 (E. Lilly Co.) in amounts of 50 μg of each PPS given separately 2 weeks apart. Serum samples were obtained prior to and 2 weeks following immunization. Pre- and postimmunization of antibody titers were compared following assays with both RIA and IHA techniques. These methods have been published previously (16, 17).

Antibody responses were compared by examination of mean fold increases (IHA and RIA), percentage responders (IHA and RIA), and pre- and postimmunization levels expressed as ng AbN/ml (RIA). The mean fold increase was determined by dividing

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the reciprocal of postimmunization titer by the reciprocal of the preimmunization IHA titer and expressed as $\log_2$ for IHA. Percentage responders were calculated by determining those individuals having antibody responses 1.4-fold and greater increases (RIA) and 1-fold or greater ($\log_2$) increase (IHA). Pre- and postimmunization titers were compared by RIA and expressed as ng AbN/ml.

Sixty-six elderly female residents of a retirement home were evaluated. Ages ranged from 57 to 100 years (mean age 78 years). All were ambulatory and free of acute illness at the time of the study. Controls consisted of 20 healthy adult employees of a medical center. Their ages ranged from 28 to 42 years (mean age 38 years).

Immunoglobulin levels were determined by radial immunodiffusion. Preimmunization samples were used for immunoglobulin assays.

Statistical analysis was performed by using geometric means of pre- and postimmunization titers determined by RIA and compared to those of controls by nonparametric analysis (Mann–Whitney). Mean fold increases of RIA and IHA postimmunization responses in the control and elderly populations were compared by nonparametric analysis (Mann–Whitney). Percentage responders determined by RIA and by IHA were compared using χ^2 analysis (two tailed) with the Yates correction factor. Statistical analysis of small numbers (less than 30) was performed by using Fisher's exact t test.

Results. The mean age of the study group was 78 years with a range of 57 to 100 years, whereas the mean age for the controls was 38 years with a range of 28 to 42 years. Determination of levels of IgG, IgM, and IgA in serum demonstrated a significant elevation of IgA in the elderly group, but no differences between the values of IgG and of IgM in the two groups (Table I). These findings are in agreement with those of previous studies (7–9).

When the elderly group was divided into two subgroups (Table II), responders and nonresponders, and when levels of immunoglobulins in the two subgroups were compared, the nonresponders had significantly lower levels of both IgA ($P < 0.005$) and IgM ($P < 0.05$). This correlation was observed for the responses to both pneumococcal polysaccharide types 3 and 8.

Mean fold increases in levels of antibodies to pneumococcal polysaccharide types 3 and 8 in the elderly and control groups, determined by IHA and RIA, were compared. With levels determined by either method, there was no significant difference between the two study groups except for levels of antibody to pneumococcal polysaccharide type 3 determined by IHA (Table III). The percentage responders, compared by IHA and RIA, showed no significant difference between the elderly and the control group (Table IV).

The elderly group had significantly lower preimmunization levels of antibody to pneumococcal polysaccharide types 3 and 8, determined by RIA, than did controls (Table V). Although the fold increases following immunization were not significantly different between the elderly group and the controls (Table III), the antibody level achieved following immunization was less for both pneumococcal polysaccharide types 3 and 8 (Table V). Only the difference between levels of antibody to pneumococcal polysaccharide 3 in the two groups was statistically significant.

Discussion. Significant impairment of immunity has been reported in aged individuals. T-cell function is diminished as evidenced by the absence of responses of delayed hypersensitivity (12, 13), involution of the thymus, and alterations in T-cell

TABLE I. COMPARISON OF IMMUNOGLOBULIN LEVELS IN ELDERLY INDIVIDUALS AND YOUNG ADULTS

	IgG (mg/100 ml)	IgM (mg/100 ml)	IgA (mg/100 ml)
Elderly group	1394 ± 356	111 ± 88	301 ± 134
Young adults	1158 ± 305	99 ± 27	200 ± 61
P value	>0.05	>0.05	<0.0005

TABLE II. COMPARISON OF IMMUNOGLOBULIN LEVELS (mg/100 ml) IN RESPONDER AND NONRESPONDER ELDERLY INDIVIDUALS

	PPS 3			PPS 8		
Elderly group	Number	IgM	IgA	Number	IgM	IgA
No titer change	6	45 ± 333	235 ± 121	14	71 ± 57	256 ± 121
Greater than one-fold increase (log_2 IHA)	60	104 ± 88	306 ± 131	52	118 ± 110	306 ± 133
P value		<0.05	<0.005		<0.05	<0.005

numbers and activity (13). Although several investigators have shown decreased numbers of cells forming E-rosettes in aged populations (19, 20), other studies have indicated that the numbers of T cells are normal (21). There have been conflicting reports regarding the lymphocyte response to mitogens and to allogenic cells (13, 22).

Antibody mediated immunity is abnormal in aged populations. Analysis of immunoglobulin levels usually demonstrates significant elevation of IgA (8, 9). Initial reports appeared in 1969 indicating that aged individuals had lower levels of antibody to viral and to bacterial antigens than did members of a control population (23). Studies of responsiveness to immunization utilizing flagellin as an antigen have shown normal total levels of antibodies but impaired ability to maintain IgA antibody levels (24). Additional studies have shown that preimmunization levels of antibody to flagellin were less in aged populations than in young adults and that older individuals attained lower titers of total antibody (IgG + IgM) after immunization (25). Our studies with pneumococcal polysaccharide are in agreement with these results and demonstrate both a decrease in pre- and postimmunization levels of antibody to pneumococcal polysaccharide types 3 and 8.

Elderly individuals have an increased susceptibility to infection with *Streptococcus pneumoniae* as well as an increased mortality (14). Previous studies in elderly populations have indicated that the response to immunization with pneumococcal polysaccharides was comparable to young adults (15). Our study indicates that there is an impaired response in advanced age (mean age 78 years) groups. Although the fraction of elderly individuals responding to immunization with a significant fold increase was the same in the younger adult group and in the elderly group as determined by the two antibody assay methods (IHA and RIA), the pre- and postimmunization levels of antibody, determined by RIA, were significantly lower in the elderly (Table V).

The cause of impaired antibody responsiveness to pneumococcal polysaccharides

TABLE III. MEAN FOLD ANTIBODY INCREASE TO PNEUMOCOCCAL CAPSULAR POLYSACCHARIDES FOLLOWING IMMUNIZATION OF ELDERLY VS YOUNG ADULT GROUPS[a]

	PPS 3	PPS 8
Mean fold increase ± SD IHA elderly group	3.4 ± 2.1	2.0 ± 2.0
Mean fold increase ± SD IHA young adult group	6.4 ± 1.9	2.8 ± 2.1
P value	<0.002	>0.14
Mean fold increase ± SD RIA elderly group	38.3 ± 67.0	22.9 ± 27.7
Mean fold increase ± SD RIA young adult group	27.4 ± 21.3	24.3 ± 43.4
P value	>0.4	>0.4

[a] IHA: indirect hemagglutination, RIA: radioimmunoassay.

TABLE IV. PERCENTAGE RESPONDERS FOLLOWING IMMUNIZATION OF ELDERLY VS YOUNG ADULT GROUPS WITH PNEUMOCOCCAL CAPSULAR POLYSACCHARIDES[a]

	PPS 3	PPS 8
% Responders IHA elderly group	89	71
% Responders IHA young adult group	100	70
P value	>0.9	>0.1
% Responders RIA elderly group	91	89
% Responders RIA young adult group	100	90
P value	>0.5	>0.01

[a] IHA: indirect hemagglutination, RIA: radioimmunoassay.

TABLE V. ANTIBODY RESPONSES TO PNEUMOCOCCAL CAPSULAR POLYSACCHARIDES IN ELDERLY VS YOUNG ADULT GROUPS (ng AbN/ml)

	PPS 3	PPS 8
Preimmunization elderly group		
RIA mean ± SD (range)[a]	38.9 ± 4.9 (0–1,862)	91.2 ± 3.3 (8–7,244)
Preimmunization young adult group		
RIA mean ± SD (range)	100.0 ± 2.8 (30–851)	316.2 ± 2.6 (70–1,820)
P value	<0.02	<0.006
Postimmunization elderly group		
RIA mean ± SD (range)	537.0 ± 7.1 (0–50,119)	912.0 ± 4.7 (40–21,380)
Postimmunization young adult group		
RIA mean ± SD (range)	2344.2 ± 2.1 (513–7079)	1513.6 ± 3.2 (107–4,786)
P value	<0.004	<0.18

[a] Mean expressed as geometric mean ± SD (range). RIA: radioimmunoassay.

in elderly individuals is not known. Previous studies have suggested that reduced levels of antibody to flagellin, a thymus dependent antigen, are the result of impaired T-helper-cell function (24, 25). Although antibody to pneumococcal polysaccharides is thought to be thymus independent in the mouse (26), there is no evidence to support this concept in man (27). In addition, recent evidence suggests that the antibody response to polysaccharides may be thymus dependent in the mouse (28).

In our study, impaired responsiveness seemed to correlate with decreased levels of IgM and IgA in the serum (Table II). This finding would suggest a primary B-cell defect, as IgM and IgA antibody production are relatively independent of thymic function. Detailed studies of specific IgG, IgM, and IgA antibody responses to pneumococcal polysaccharide need to be performed, however, for more precise correlations to be made.

Although the levels of antibody achieved following immunization with pneumococcal polysaccharides in the elderly individuals were less than those in the younger adults (Table V), the mean level achieved was in the range which should offer protection against infection (29). This observation, coupled with the demonstration that the response rate of elderly individuals is the same as that in the controls (Table IV), suggests that immunization with pneumococcal polysaccharides in elderly populations would be effective in preventing infection with *S. pneumoniae*.

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