Immune Function and Vaccine Responses in Healthy Advanced Elderly Patients

Paul J. Carson, MD; Kristin L. Nichol, MD; James O’Brien; Pierre Hilo; Edward N. Janoff, MD

Background: Decline in immune function has been reported to predictably accompany advancing age. However, to our knowledge, few studies have specifically characterized the rapidly expanding advanced elderly population or controlled adequately for concurrent diseases.

Objective: To assess whether successfully reaching an advanced age in good health is associated with preserved immune function.

Methods: We prospectively compared in vivo with in vitro variables of immune function in 29 healthy, independently living elderly subjects (mean age, 80 years; age range, 75-103 years) and in 21 healthy young control subjects (mean age, 29 years; age range, 25-35 years) in a Veterans Affairs Medical Center.

Results: In vivo, among elderly and young subjects, numbers of total white blood cells, monocytes, lymphocytes, and lymphocyte subsets (CD4+ and CD8+ T lymphocytes and CD20+ B cells) were similar, as were levels of total serum IgG and IgM. Only levels of serum IgA were higher in the elderly subjects (3.0 vs 1.7 g/L; P = .001). Functionally, both groups showed vigorous responses to protein (tetanus and diphtheria toxoids) and polysaccharide (23-valent pneumococcal) vaccines. Although levels varied, the fold increases in vaccine antigen-specific IgG were not significantly different in young and elderly subjects, and the avidities of IgG to pneumococcal polysaccharides 14 and 19F were similar before and after vaccination. In vitro, proliferative responses of blood mononuclear cells to T-lymphocyte and B-cell mitogens ( pokeweed mitogen, Staphylococcus aureus Cowan strain I, and S aureus Cowan strain 1 plus interleukin 2 ), and lipopolysaccharide-induced production of tumor necrosis factor α , were comparable in elderly vs young subjects.

Conclusion: Successful aging, defined by reaching an advanced age with one’s overall health intact, may be associated with preserved immune function and adequate responses to vaccines.

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The “oldest old” persons, those older than 85 years, constitute the most rapidly growing segment of our population. From 1960 to 1990, the number of Americans aged 85 years or older more than doubled, more than twice the rate of increase among persons older than 65 years and 6 times that of the total population. By the year 2040, estimates propose that 8 to 13 million Americans will be older than 85 years. The high prevalence of morbidity and mortality among this group is estimated to have a tremendous impact on future health care costs. Understanding the aging process and its physiologic consequences is of paramount importance in identifying and meeting the health care challenges posed by our growing elderly population.

Gerontological research on immune function during the past several decades has focused on the inherent loss of immunologic integrity associated with aging per se. Some researchers have suggested that a decline in immune function predictably accompanies the aging process, and even that immunosenescence itself may be a cause of aging. Elderly persons experience increased rates of malignant neoplasms and accelerating rates of infections with age, consistent with declining immunity and immunosurveillance over time. Investigators have most consistently identified abnormalities in the cell-mediated arm of immunity in elderly subjects. More specifically, decreased lymphocyte responses to mitogens, loss of delayed-type hypersensitivity, decreased production and responsiveness to interleukin (IL) 2, and increases in memory cells with concomitant loss of naïve precursor cells are most commonly reported. Whether alterations in B-cell function and humoral immunity occur predictably in elderly persons is less clear, but several investigators report lowered antibody responses to vaccines and relative increases in total IgG and IgA levels.
SUBJECTS AND METHODS

SUBJECTS

Elderly subjects older than 75 years were recruited from the Veterans Affairs Medical Center, Minneapolis, Minn, general internal medicine clinic; a community outreach influenza vaccination clinic; and a hospital volunteer pool. Subjects had to be living independently and in overall good health. Subjects were excluded for any history of major medical disease (diabetes, cancer, collagen-vascular disease, or chronic diseases of the lung, heart, liver, or kidney), taking immunosuppressive medications, smoking, alcohol abuse, hospitalization within the previous year, any lower respiratory tract infection within the preceding year, or receipt of a pneumococcal polysaccharide immunization (by history and medical record review). Healthy control subjects aged 25 to 35 years were recruited from hospital and laboratory employees with similar exclusion criteria. Six elderly and 7 young control subjects who had received a tetanus toxoid (TT)–diphtheria toxoid (DT) booster in the previous 10 years were excluded from the tetanus-diphtheria immunization arm of the study. Written informed consent was obtained from each subject in protocols approved by the Veterans Affairs Medical Center Human Subjects Committee in compliance with Department of Health and Human Services guidelines.

IMMUNIZATION

Each subject was given an intradeltoid injection of 0.5 mL of aluminum phosphate–adsorbed ultrafine TT and DT (Wyeth Laboratories Inc, Marietta, Pa) and 0.5 mL of a 23-valent pneumococcal polysaccharide (Pnu-Imune; Lederle Laboratories, Pearl River, NY) on the same day in separate arms. Vaccines from the same lots were used for subjects and controls. Serum samples were collected from all subjects before and 4 weeks after vaccination. All serum samples were stored at −20°C until testing.

CELL POPULATIONS

Total leukocyte, monocyte, and lymphocyte counts were determined by an automated counter (model ZBI; Coulter Electronics, Inc, Hialeah, Fla). Peripheral blood mononuclear cells were separated on a gradient (Ficoll-Hypaque; Sigma-Aldrich Corp, St Louis, Mo). Peripheral blood T-lymphocyte and B-cell subsets were then measured on enrollment into the study by fluorescence-activated cell sorter analysis (FACS model 440; Becton Dickinson Immunocytometry Systems, Inc, Mountain View, Calif) with murine monoclonal antibodies to T lymphocytes (CD3, CD4, and CD8) and B cells (CD20) (Becton Dickinson Immunocytometry Systems, Inc) with appropriate isotype control antibodies.

ANTIBODY MEASUREMENTS AND AVIDITY

Levels of total serum IgG, IgM, and IgA were measured by nephelometry. Levels of pneumococcal capsular polysaccharide–specific IgG for vaccine serotypes that commonly cause invasive disease in elderly persons (types 4, 8, 12F, 14, and 19F) and TT- and DT-specific IgG in serum were measured by enzyme-linked immunosorbent assay exactly as previously described.20-28 Coefficients of variation

RESULTS

CLINICAL

Measures of absolute leukocyte, monocyte, and lymphocyte subset analysis by fluorescence-activated cell sorting showed no differences between the young and elderly subjects (Table 1). Only levels of total IgA, but not IgG or IgM, in serum were increased among the elderly subjects.

IN VIVO

Humoral responses to pneumococcal polysaccharide and protein (TT and DT) antigens were measured in serum before and 4 weeks after vaccination. Compared with preimmunization values, older subjects generated a significant increase in IgG to 4 of 5 common pneumococcal capsular polysaccharides (types 4, 8, 12F, and 14) following immunization with the recommended 23-valent vaccine, as did young adults (types 4, 8, 14, and 19F) (Table 2). Neither preimmunization nor postimmunization levels of capsule-specific antibody were significantly different between the 2 age groups, nor were mean fold increases in IgG to these polysaccharides.

In addition to levels of antibody, the avidity, or functional affinity, of antibodies may contribute to their protective effects. Avidity, a quality related to the strength of antigen-antibody binding, may influence the ability of antibodies to mediate killing of encapsulated organisms.20,29,31-38 Before and following immunization, the avidity of pneumococcal capsule–specific IgG was similar among young adults and healthy advanced elderly subjects (Figure 1). Although the
avidity of antibodies for type 14 did not change following immunization in either group, avidities for type 19F antibodies did increase significantly in both age groups. Whereas only 11% of each group showed greater than a 2-fold increase in the avidity index for type 14 after immunization, 22% of the elderly subjects and 35% of the young adults exceeded this threshold for type 19F. Such substantial changes in avidity have been shown in children immunized with pneumococcal polysaccharides for type B, but they have not been described previously in adults immunized with pneumococcal polysaccharides. When analyzed by sex, avidities for type 19F antibodies were higher among elderly men than among young men or older women before immunization (P<.02; avidity index, 0.67±0.09 vs 0.33±0.03 or 0.40±0.05, respectively). No differences in avidity were observed between groups for type 14 or 19F after immunization. Thus, levels and functional affinity of antibodies to pneumococcal polysaccharides were quite comparable among healthy young and healthy advanced elderly adults.

Similar to results with pneumococcal polysaccharide vaccine, elderly subjects generated significant humoral responses to recall protein antigens TT and DT (Figure 2). However, when compared with the younger control group, elderly subjects had signifi-

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### Table 1. Clinical and Immunological Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Advanced</th>
<th>Elderly</th>
<th>Young</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean ± SD</td>
<td>80.0 ± 6.0</td>
<td>29.0 ± 3.3</td>
</tr>
<tr>
<td>Range</td>
<td>76-103</td>
<td>25-35</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Cell count, x10/L*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total leukocytes</td>
<td>6.10 ± 0.30</td>
<td>5.90 ± 0.40</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.67 ± 0.12</td>
<td>1.76 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.52 ± 0.028</td>
<td>0.52 ± 0.040</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subset, cells/µL*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ T lymphocytes</td>
<td>668 ± 53</td>
<td>728 ± 66</td>
<td></td>
</tr>
<tr>
<td>CD8+ T lymphocytes</td>
<td>352 ± 39</td>
<td>401 ± 44</td>
<td></td>
</tr>
<tr>
<td>CD20+ B cells</td>
<td>115 ± 13</td>
<td>132 ± 13</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin level, g/L*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>11.66 ± 0.55</td>
<td>10.87 ± 0.57</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>1.34 ± 0.15</td>
<td>1.57 ± 0.14</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>3.02 ± 0.32</td>
<td>1.69 ± 0.15*</td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as mean ± SEM.
†P < .003 compared with the elderly participants.
cantly lower prevaccine levels of TT-specific antibodies (P < .01), and convalescent levels for TT- and DT-specific antibodies tended to be lower in the elderly subjects (P = .06). Despite these lower absolute levels in the elderly subjects, the ability to generate a response on antigenic challenge (eg, mean fold increase in TT- and DT-specific antibodies) was comparable or greater in the elderly subjects (P = .02 for TT-specific IgG). Moreover, the absolute increase in antibody to TT (50.3 ± 11.1 vs 65.5 ± 14.4 µg/mL) and DT (6.2 ± 2.2 vs 11.8 ± 0.3 µg/mL) was comparable in the elderly subjects and in young adults, respectively. Thus, static measures of immune competence (cell numbers and lymphocyte subset distributions) and the functional immune reserve (responsiveness to vaccines) were rela-

tively intact in the healthy advanced elderly subjects compared with those in younger adults.

IN VITRO

Results of in vitro tests of immune function complemented those in vivo. Peripheral blood mononuclear cells from the elderly subjects showed a robust proliferative response to T-lymphocyte and B-cell mitogens (pokeweed mitogen and SAC, respectively) that paralleled that of young subjects (Figure 3, top). Moreover, although the elderly subjects have been described to show impaired responses to the T-lymphocyte–derived lymphotrophic cytokine IL-2,40,41 this factor was equally effective in augmenting proliferative responses to SAC in both age groups at the concentration tested (20 U/mL). Immunoglobulin production also increased significantly and com-
pared with those in younger adults.

Figure 2. IgG responses in serum to protein recall antigens tetanus toxoid (TT) (top) and diphtheria toxoid (DT) (bottom) in 23 elderly subjects and 14 young adults before and 1 month after immunization. Results are shown as mean ± SEM.

Table 2. Antibody Responses to Specific Pneumococcal Vaccine Serotypes

<table>
<thead>
<tr>
<th>Capsular Serotype</th>
<th>Before Immunization</th>
<th>After Immunization</th>
<th>Fold Increase</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>TT-specific IgG, g/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Young Adults (n = 18)</td>
<td>Elderly Adults (n = 28)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.87 ± 1.53</td>
<td>6.38 ± 1.53</td>
<td>1.10</td>
</tr>
<tr>
<td>1</td>
<td>25.79 ± 7.49*</td>
<td>18.61 ± 5.82*</td>
<td>0.72*</td>
</tr>
<tr>
<td>8</td>
<td>1.84 ± 0.83</td>
<td>1.93 ± 0.80</td>
<td>1.05</td>
</tr>
<tr>
<td>12F</td>
<td>23.90 ± 6.14*</td>
<td>12.16 ± 4.62*</td>
<td>0.51*</td>
</tr>
<tr>
<td>14</td>
<td>57.41 ± 10.03</td>
<td>180.85 ± 93.04</td>
<td>3.16</td>
</tr>
<tr>
<td>1</td>
<td>301.08 ± 10.53</td>
<td>328.81 ± 103.59</td>
<td>1.09</td>
</tr>
<tr>
<td>12F</td>
<td>3.97 ± 1.17</td>
<td>9.44 ± 3.32</td>
<td>2.39</td>
</tr>
<tr>
<td>1</td>
<td>34.31 ± 19.20</td>
<td>20.76 ± 4.77</td>
<td>0.65</td>
</tr>
<tr>
<td>14</td>
<td>5.87 ± 1.53</td>
<td>6.38 ± 1.53</td>
<td>1.10</td>
</tr>
<tr>
<td>1</td>
<td>301.08 ± 10.53</td>
<td>328.81 ± 103.59</td>
<td>1.09</td>
</tr>
<tr>
<td>19F</td>
<td>5.5 ± 1.1</td>
<td>3.6 ± 0.9</td>
<td>0.65</td>
</tr>
<tr>
<td>1</td>
<td>59.34 ± 8.97</td>
<td>85.01 ± 11.74</td>
<td>1.45</td>
</tr>
<tr>
<td>19F</td>
<td>150.10 ± 29.67*</td>
<td>301.57 ± 117.17</td>
<td>1.99*</td>
</tr>
<tr>
<td>Fold increase</td>
<td>12.9 ± 2.3</td>
<td>7.6 ± 1.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*p < .05 compared with prevaccine values by the paired t test.
phocytes, and their subsets (B cells and CD4+ and CD8+ T lymphocytes). Only levels of serum IgA were in-
creased, as variably reported in the literature.3,10,18,24,43 Such perturbations of B-cell activation. Deficits in cell-
mediated immunity, as evidenced by poor lymphocyte responses to mitogens, have been one of the more con-
sistent abnormalities described in elderly persons, par-
ticularly with T-lymphocyte mitogens.3,5,10,41,44,45 This de-
fect has been hypothesized to be due, in part, to decreased

We have shown that a range of immune functions were relatively intact in a healthy group of advanced elderly subjects compared with those in young adults 50 years their junior. In almost all areas of in vitro, in vivo, and clinical examination, including responses to vaccine, we found few statistically significant differences between the 2 groups. Consistent with previous observations, aging did not appear to affect absolute numbers of most cell lines,3,5,10,42 including the number of monocytes, lymphocytes, and their subsets (B cells and CD4+ and CD8+ T lymphocytes). Only levels of serum IgA were increased, as variably reported in the literature.3,10,18,24,45 Such polyclonal elevations may result from cumulative antigen exposure over time, increased mucosal exposure, or perturbations of B-cell activation. Deficits in cell-mediated immunity, as evidenced by poor lymphocyte responses to mitogens, have been one of the more consistent abnormalities described in elderly persons, particularly with T-lymphocyte mitogens.3,5,10,41,44,45 This defect has been hypothesized to be due, in part, to decreased

production of and response to IL-2, a crucial growth fac-
tor for lymphocyte proliferation to mitogen or antigen, and dysregulation of activation requirements.14,15,46,47 However, in the healthy advanced elderly persons described herein, proliferative responses to T-lymphocyte (pokeweed) and B-cell (SAC) mitogens were intact. Furthermore, elderly and young subjects showed comparable proliferative responses with IL-2 supplementation. In each case, optimal doses of mitogen or IL-2 were used; dose responses may have revealed more subtle de-

Aside from the IL-2–related responses noted, to our knowledge, few studies have examined other cytokine responses in elderly humans. Interleukin 1 production has been normal or decreased in elderly per-
sons, whereas TNF-α levels were elevated in the serum samples from elderly subjects in one study48 but produc-
tion of TNF-α in vitro was normal when compared with young subjects in another.44,48-50 We showed that in vitro production of TNF-α, a key cytokine in the immediate inflammatory response to infection, by peripheral blood mononuclear cells with and without stimulation with lipopolysaccharide was not appreciably affected by age. These data are consistent with limited previously published data51 from this group of elderly and young subjects, among whom plasma levels of TNF-α, IL-6, IL-10, and transforming growth factor β were all comparable.

Perhaps the greatest relevance of these data to the care of advanced elderly adults is their responses to these recommended vaccines. That prevaccine levels of TT-specific antibodies were lower in the elderly subjects com-
pared with the younger adults likely reflects the longer intervals since the former’s last immunization. In some cases, subjects had not been immunized since their military service in World War II, and others were uncertain if they had ever even received a primary immunization series. Despite these limitations, advanced elderly sub-
jects showed vigorous responses to immunization with TT and overall higher mean fold increases in TT-
specific antibodies compared with those in younger adults. This pattern of response was similar to that seen with DT. Earlier studies10,22 reporting lower responses to immu-

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groups of debilitated advanced older adults with under-
specific antibodies correlates with their ability to mediate
body avidity. The avidity, or functional affinity, of capsule-
the duration of antibody responses, but we did charac-
terization against pneumococcal disease. We did not address
an important determinant of vaccine-derived protec-
This peak value, and the persistence of the antibodies, is
saccharides tended to be lower among elderly subjects,
healthy subjects.
say for antibody measurement) and to our selection of
differences in methods (23- vs 14-valent vaccine and en-
zyme-linked immunosorbent assay vs radioimmunoas-
say for antibody measurement) and to our selection of
healthy subjects. Although mean fold increases to pneumococcal poly-
saccharides tended to be lower among elderly subjects, the peak levels at 1 month were not significantly lower. This peak value, and the persistence of the antibodies, is an important determinant of vaccine-derived protec-
tion against pneumococcal disease. We did not address the duration of antibody responses, but we did charac-
terize the quality of the antibodies produced, or anti-
body avidity. The avidity, or functional affinity, of capsule-
specific antibodies correlates with their ability to mediate complement-dependent killing of the organisms by phagocytes. In this context, healthy advanced el-
derly adults were also able to generate antibodies with functional affinity comparable with those of healthy young adults.

Overall, these results may have implications for clini-
cal practice as it pertains to adult immunization. De-
spite the universal recommendation for pneumococcal vaccination in persons older than 65 years, vaccination rates in the United States for this group have tended to be poor, at 25% to 50%. These low rates are believed to be due, in part, to the widespread perception that pneu-
ococcal vaccine is poorly immunogenic in elderly per-
s. Although our study does not purport to suggest clinical efficacy, it does suggest that advanced age per se may not be a risk factor for lowered immune re-
sponses. Limitations in our data include that, as noted, we did not assess the duration of these antibody re-
sponses. Indeed, some investigators have found that responses to various vaccines may be less long lasting among elderly persons. However, consistent with our re-
results, a recent study of responses to pneumococcal vac-
cine in elderly persons found comparable avidity and du-
rability of capsule-specific IgG antibodies in most elderly subjects and in younger control subjects. In addition, we did not measure the ability of these serum samples to me-
diate killing of \textit{S pneumoniae} by phagocytes in vitro, and groups of debilitated advanced older adults with under-
lying illness showed impaired phagocytic activity in vitro. These data in healthy advanced elderly adults would lend support to the several retrospective case-control studies that do suggest vaccine efficacy in this patient popu-
lation against serious pneumonia and invasive \textit{S pneumoniae} infections, although controlled data of efficacy against all pneumococcal pneumonia in older adults are more limited.

Our findings challenge the conventional notions of inherent immunesenescence. These contrasting results are likely explained in large part by differences in sub-
ject selection. Prior studies have varied considerably in the definition of “elderly” and “healthy” subjects. Many recruited healthy elderly subjects from clinics and nurs-
ing homes and did not specify strict case definitions and rarely included any discussion of other factors (under-
lying illnesses, medications, vitamins, smoking, or alco-
hol use) that may affect immune function. We used rig-
orous screening for potential immune-altering medications and comorbidities. Our data are somewhat limited by ex-
amination of a small, highly selected sample of healthy older adults and may not be readily generalizable to a large segment of the elderly population. Similarly, we cannot extrapolate these results to predict responses to other vaccines commonly used in elderly persons, such as the influenza virus vaccine or, more recently considered, the varicella vaccine. However, our re-
results emphasize the need to more systematically charac-
terize the impact of comorbidity and other factors that may contribute to the aging process as causes of immu-
escences.

Comorbidity has been a neglected area of investiga-
tion in studies of immune function in elderly per-
s. Although nutritional assessment was not available in our group of healthy advanced elderly adults, several variables of immune function were reported to be worse among elderly subjects with regular clinic visits for health problems than among healthy elderly subjects. Indeed, factors such as diet, exercise, personal habits, and psychosocial stress are often overlooked when studying “normal” physiologic losses associated with aging. Nutrition, including protein undernutrition and deficiencies of vitamins and trace elements, may underlie many immune deficits attributed to age. The association of vitamin B12, deficiency with impaired responses to pneu-
ococcal polysaccharide vaccination in elderly persons highlights that cofactors may contribute to immune in-
tegrity or dysregulation more than putative prepro-
grammed immunesenescence.

In summary, we have shown that in a group of healthy advanced elderly individuals, several measures of immune function remain essentially intact when com-
pared with those in healthy adults 50 years younger. A prominent component of this immune competence is their ability to generate robust antibody responses to the panel of vaccine antigens tested. Our subjects represent a distinct subgroup of people who successfully reach an advanced age with their overall health intact. Our study did not measure all possible components of immune func-
tion and was not designed to establish primacy between functional immunity and attaining “healthy advanced el-
derly” status. Indeed, these data raise the question as to
whether immunocompetence leads to or derives from overall good health and longevity, and what role genetics and environment play on these outcomes. Answers to these questions require long-term prospective longitudinal studies in which immune function and clinical outcome in a large cohort are monitored over time. Such investigations should characterize the roles of illness (co-morbidity), nutrition, and stress on the development of immunosenescence or on the immunologic vitality of advanced elderly persons.

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