Alleged Susceptibility of the Elderly to Infection

PAUL B. BEESON, M.D.

Professor of Medicine, Emeritus, University of Washington, Seattle, Washington

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The widely held notion, common in clinical medicine, that the elderly are more susceptible to infection is discussed critically. Implied but unstated in this sentiment is a premise that host defense mechanisms are less effective in the elderly, or that immune surveillance becomes defective with aging. No clear evidence exists to support these concepts; indeed, available information points to a normally functioning immune system in the elderly. An increased incidence of morbidity and mortality resulting from infection in the elderly does exist, however, and it is suggested that this stems from many of the functional and anatomical deficits which accompany the aging process and therefore predispose the elderly to infection. Examples of these degenerative problems are pulmonary hypoventilation, bronchopulmonary aspiration, immobility, and urinary retention. These conditions can predispose the elderly to infection by common extracellular microorganisms that are the normal flora of the mucosal and skin surfaces of the body. More precise information on the nature of injuries caused by these organisms in the elderly and on the causes of the resulting higher mortality rates in the elderly is required before an increased incidence of infection in the elderly can be attributed to an increase in their susceptibility to infection because of defective immune or host defense mechanisms.

I propose here to examine critically the widely held notion that the elderly are susceptible to infections. This has served, and still is serving, as a basic premise for a considerable amount of laboratory investigation.

No one can question that certain kinds of infection occur frequently in people of advanced age, that these infections cause morbidity, or that they frequently constitute terminal illnesses. My reasons for "attacking a straw man" are twofold: first, the word "infections" is too all-encompassing; second, there is an implication that host defense mechanisms have a tendency to deteriorate during the aging process.

As to the first, are we to accept the notion that old people are increasingly liable to disease due to viruses, bacteria, fungi, and metazoon parasites? And, second, what are we to make of the muddy term "susceptibility"? Does its use lead us to expect a defect in phagocytic power, macrophage function, lymphocyte function, antibody production, or complement activity?

I believe that in saying that the elderly are "susceptible to infection" there is an unstated assumption that defective immune surveillance, a concept invoked to explain the increased incidence of neoplastic diseases in old age, also applies to host defense mechanisms.

There are some points about infection in the elderly for which there is ample evidence:

The etiologic agents responsible for most infections in old people are the common extracellular microorganisms which comprise the normal flora of the skin, mouth, respiratory passages, and gut.
The tissues they invade, and the type of damage they do, are the same in old as in young human beings.
The clinical manifestations of these common infections differ in the elderly only in that the inflammatory reaction is less intense, so that local tenderness and such systemic manifestations as fever may be less conspicuous [1]. The outcome of these common infections tends to be more grave in the elderly. Old people retain their immunity to the common infections of childhood; furthermore, they appear to be less frequently affected by common viral respiratory disease.

**THE IMMUNE SYSTEM IN OLD AGE**

Much work has been devoted to the study of the function of various components of the immune system in elderly subjects—both human and animal. There are indeed measurable changes, which can be summarized as follows:

The thymus undergoes involution after middle age, and the thymic hormone can no longer be demonstrated in the blood after about age 50. The T-lymphocyte population, while numerically unchanged, contains a larger proportion of undifferentiated cells: fewer committed helper cells, suppressor cells, and effector cells. These changes are evidenced by diminished cell-mediated immune responsiveness, greater numbers of autoimmune antibodies, and lessened cytotoxic activity. B-lymphocytes are about the same in number, but antibody responses are of lower magnitude and shorter duration. Phagocytic activity by polymorphonuclear leukocytes and macrophages shows little change, and, as well as can be tested, the fixed phagocytes of the reticuloendothelial system are working normally. There are no substantial alterations in complement activity.

**IS THERE CLINICAL EVIDENCE OF DEFECTIVE IMMUNE SURVEILLANCE AGAINST PREVIOUSLY ACQUIRED INFECTIONS?**

*Tuberculosis*

Let us remind ourselves first that until recent decades, relapse of previously acquired tuberculosis was seen mainly in young adults. Unquestionably there has been a rise in the age incidence of active tuberculosis lately [2]. In part this may relate to a greater prevalence of tuberculosis several decades ago, when today's old people were young; to some extent it reflects the higher proportion of people now living to old age. In part also, the high rate of tuberculosis in elderly people residing in nursing homes has features of nosocomial infection [3].

*Syphilis*

The late manifestations (gumma, aortic disease, central nervous system disease) usually develop in the age period between 30 and 50.

*Measles*

Exacerbation of previously acquired measles, in the form of subacute sclerosing panencephalitis, usually occurs in the age period between four and 20.

*Rickettsial Infections*

Relapse of louse-born typhus fever (Brill's disease) as studied by Zinsser showed that 65 percent of recrudescences occurred before age 40, and 80 percent before age 50 [4].
Herpes zoster

This infection seems the most likely candidate to show that defective immune surveillance accounts for its frequency in the elderly. The attack rate does increase with age (though it is not a real rarity in people under age 50). It has a well-known association with Hodgkin’s disease, in which defective immune responses are characteristic [5]. Still, there are reasons to question whether defective immune surveillance is the key to the age-related incidence of herpes zoster. First of all, what about the characteristic zonal distribution of the lesions? That raises the possibility that some local structural factor, rather than a general failure of immune function, permits proliferation of the virus in one or two dermatomes. The specific viral sequences of varicella/zoster have been demonstrated in samples of sensory ganglia of normal individuals who had not recently suffered from varicella or zoster [6], substantiating the supposition that the varicella agent remains in such tissues for long periods of time. The explosive revival of viral proliferation confined to single nerve roots suggests that local factors may be responsible, rather than some general breakdown in host resistance. This finds some support in records of the occurrence of zoster following local irradiation therapy, as for cancer of the breast [7]. Generalized zoster is known to be associated with chronic lymphocytic leukemia. It is also worth noting that people who suffer from herpes zoster do not exhibit increased risk of developing cancer [8].

So, no persuasive, all-embracing case can be made for postulating that decline in immune function is responsible for flare-ups of quiescent infections in old people.

ARE OPPORTUNISTIC INFECTIONS A SPECIAL PROBLEM OF THE ELDERLY?

If there were a major defect in immune functions in old people, one might expect them to be subject to opportunistic infections due to fungi, pneumocystis, toxoplasma, and cytomegalovirus. These, together with Kaposi’s sarcoma, are problems of patients with AIDS. They occur in children and throughout adult life but are not notably prevalent in the elderly.

FACTORS WHICH DO CONTRIBUTE TO BACTERIAL INFECTIONS IN THE ELDERLY

The aged are afflicted by chronic diseases, along with the functional decrements that accompany the aging process. These, simply or in concert, create conditions that favor tissue invasion by bacteria normally present in, or on the surface of, the body. That is to say, the infections that are the special problem of the elderly occur as complications of anatomical and functional changes coincident with aging or with diseases that are more common in the elderly. Let us survey some samples.

Respiratory Tract

Chronic bronchitis, due to use of tobacco or inhalation of particulate matter, sets the stage for superimposed bacterial infection, including pneumonia. Patients who have suffered strokes may have diminished pulmonary ventilation, their cough reflexes may be depressed, and they are liable to aspirate oropharyngeal contents.

Urinary Tract

Incomplete bladder emptying is common in old women, due to relaxation of supporting structures around the bladder; residual urine provides opportunity for
multiplication of any bacteria which gain entry via the urethra. In old men prostatic disease causes obstructive uropathy and incomplete bladder emptying and exposes them to the risks of urethral instrumentation.

**Immobility**

Immobility, due to stroke or severe musculoskeletal disease, may contribute to hypercalciuria, urinary stone formation, and urinary tract infections. It also favors development of pressure necrosis and decubitus ulcers, which usually become infected.

**Skin and Mucosal Surfaces**

The skin is thinner in the elderly, more liable to ulceration and delayed wound healing, especially where there is maceration due to urinary and fecal incontinence. Mucosal surfaces become thin, and there is some evidence that bacterial adherence to the lining cells is favored.

**Malnutrition**

For many reasons old people may eat poorly—because of dental problems, inability to shop for food, loss of taste, and co-existence of painful diseases such as neoplasm or musculoskeletal disorders. They may become deficient in protein and other essential nutrients.

**Neoplastic Diseases**

Tumors obstruct the outflow of secretions from the biliary tract, the respiratory tract, or the urinary tract, thus favoring occurrence of intractable infections in obstructed organs. A few neoplastic diseases—chronic lymphocytic leukemia and multiple myeloma—affect immunoglobulin synthesis, accounting for an increased liability to pneumococcal infections.

**Digestive Disorders**

Intestinal diverticula become more common with increasing age; thus diverticulitis is encountered mainly after middle age. Gall stones increase in frequency with each decade of life, and the presence of these foreign bodies as well as their capacity to cause obstruction increases the chance of suppurative cholecystitis or cholangitis.

**Diabetes Mellitus**

The incidence increases with the years. Diabetics are likely to have the urinary bladder catheterized, and their associated vascular disease causes infection to be a more serious problem in the kidneys and in the feet. Sugar in the urine makes women prey to fungal infections of the vulva.

**Peripheral Vascular Disease**

Along with impaired blood flow to the feet there may be impairment of sensory function, which increases the chance of skin injury, thus providing opportunity for infections to spread into deeper tissues.

**Environmental Exposure**

Elderly people spend a greater portion of their lives in hospitals and nursing homes, where they are subject to nosocomial infections.
The foregoing illustrates my reason for challenging the proclamation that the elderly are "susceptible to infections." Part of the confusion results from our tendency to link "hard" and "soft" data. The assumption that an age-related association of death from pneumonia means that the elderly are "susceptible" to pneumonia links age and death ("hard") with the unknown train of events leading to pneumonia ("soft"). Feinstein has discussed the pitfalls of this kind of statistical flaw [9]. Perhaps thinking would be clearer if we were to use the word "liability" instead of the word "susceptibility."

**GREATER VULNERABILITY OF THE ELDERLY TO THE EFFECTS OF INFECTION**

Most specific infections are more likely to kill old people than young adults. After early childhood, the death rate in any series of cases of pneumonia, meningitis, encephalitis, infective endocarditis, dysentery, or influenza always appears to be higher in people beyond the age of 60 years.

This confronts us with a vast area of ignorance: why do infections cause death of the host. We, of course, understand something about it in the cases of exotoxin-producing organisms and of viruses. The manifestations of, say, diphtheria or tetanus, can be reproduced experimentally by toxins obtained from cultures of the causative organisms. And we are justified in assuming that the multiplication of viruses within a cell can affect the life of that cell in such a way as to cause its death.

But when we turn our attention to the organisms that cause most infections in old people, we simply cannot indicate the nature of the harmful effect. For instance, the pneumococcus, a dangerous extracellular pathogen in patients of any age, when tested in the laboratory exhibits little or no content of injurious substances. Furthermore, none of our clinical laboratory tests tells us why people die of pneumonia.

Despite all of the studies that have been devoted to the endotoxins of gram-negative bacteria, we are hard put to attribute the clinical manifestations of diseases caused by endotoxin-producing organisms to their direct effect. The same can be said of such well-studied bacterial products as fibrinolysins and hemolysins.

Yet there can be no question about the increased vulnerability of the elderly to common infections. I would like to illustrate this by reproducing a figure (Fig. 1) published with Westerman in the *British Medical Journal* 40 years ago [10]. An epidemic of meningococcal meningitis had occurred in Britain in 1940, causing several thousand cases of the disease. In 1941, an official of the Ministry of Health turned 3,575 case records over to me for analysis. Presumably the epidemic had been caused by one meningococcal strain, and also the only treatment available at that time was the sulfonamide group of drugs. Thus this series was ideal for testing the vulnerability of people according to age. There were substantial numbers of cases in every age bracket, even 76 persons older than age 60.

As may be seen in Fig. 1 the fatality rate was high in infants and young children but fell to only about 6 percent during the period between ages 15 and 19, after which it rose steadily, reaching nearly 60 percent, despite the same antimicrobial treatment, in people over age 60. The fact I wish to draw special attention to is that the mortality rate began to rise in the late 20s, and became higher thereafter. Thus this vulnerability is not something that abruptly makes its appearance at the time of supposed failure of immune surveillance. If a similarly large and uniformly treated series of cases were duplicated in the instance of many other specific infections, I am sure the trend would be similar. This kind of age-associated vulnerability holds for other kinds of diseases,
for example, pulmonary infarction, myocardial infarction, or massive gastric bleeding. We lack a precise understanding of the increasing vulnerability of the elderly to cope with all these different kinds of stress.

Incidentally, one could use the data in the figure to argue that older people are less likely to acquire meningococcal meningitis than younger people. In one-quarter of the cases the patients were under five years of age, and approximately one-tenth were in each five-year bracket through age 29. By contrast, only about 2 percent of the cases were in the five-year groups from 50 to 60, and all people over age 60 constituted only 2.1 percent of the total series.

To summarize, then, the infections that are common and important in the elderly are due to common extracellular microorganisms that are normal flora of mucosal surfaces and the skin.

There is little clinical evidence to support a concept that failure of immune surveillance causes increased liability to the types of infections that comprise the important clinical problems in people of advanced age.

The process of aging carries with it a liability to chronic diseases and to degenerative changes in organ systems, which induce such phenomena as urinary retention, biliary tract obstruction, pulmonary hypventilation, bronchopulmonary aspiration, immobility, and paralysis, exposing subjects to liability to infection by microorganisms normally present in or on the body.

We lack precise information on: (1) the nature of the injury caused by extracellular pathogens; (2) the reasons elderly people are more likely to die from this kind of infectious disease; and (3) why old people often exhibit fewer clinical manifestations of inflammation, including fever.

With regard to the third item above, there may be a lead in the fact that patients with uremia sometimes exhibit few clinical signs of inflammation and also may be afebrile, when suppurative infection is present [11].
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