

## Clinical Experience

# First Autopsy Study of an Okinawan Centenarian: Absence of Many Age-Related Diseases

Adam M. Bernstein,<sup>1</sup> Bradley J. Willcox,<sup>2</sup> Hitoshi Tamaki,<sup>3</sup> Nobuyoshi Kunishima,<sup>4</sup> Makoto Suzuki,<sup>5</sup>  
D. Craig Willcox,<sup>6</sup> Ji-Suk Kristen Yoo,<sup>7</sup> and Thomas T. Perls<sup>8</sup>

<sup>1</sup>Department of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.

<sup>2</sup>Pacific Health Research Institute and the Department of Geriatrics, John A. Burns School of Medicine, University of Hawaii, Honolulu.

<sup>3</sup>Department of Internal Medicine, Chubu Hospital, Okinawa, Japan.

<sup>4</sup>Department of Pathology, Chubu Hospital, Okinawa, Japan.

<sup>5</sup>Okinawa Research Center for Longevity Science, Okinawa International University, Japan.

<sup>6</sup>Okinawa Prefectural University, College of Nursing, Japan.

<sup>7</sup>Wellesley College, Massachusetts.

<sup>8</sup>Boston University School of Medicine and Boston Medical Center, Massachusetts.

Consistent with the compression-of-morbidity hypothesis, several studies have reported that a significant proportion of centenarians delay or escape age-related diseases. Of those who live with such diseases for a long time, many appear to do so with better functional status than do younger persons who do not achieve extreme old age. The authors describe the first autopsy in an Okinawan-Japanese centenarian who escaped many age-related illnesses and delayed frailty toward the end of her very long life. Her late-life morbidity pattern is contrasted with that of white centenarians.

**I**N Okinawa, a Japanese prefecture, life expectancy at birth is 81.8 years, among the longest in Japan, the world's longest-lived country at 81.2 years, and 5 years longer than that in the United States at 76.8 years (1,2). The prevalence of and mortality from many age-associated diseases in Okinawa, such as cardiovascular diseases and cancer, appear to be lower than those in Japan and the United States (1,2). We wondered to what extent are exceptionally long-lived survivors in Okinawa, such as centenarians, burdened by chronic diseases, and to what extent do their lives reflect the compression-of-morbidity model.

To answer these questions, careful premortem and postmortem phenotyping of exceptional survivors is required, yet few autopsy studies of centenarians exist in the United States or elsewhere. This is the first report of an autopsy performed on a centenarian in Okinawa, Japan. The autopsy findings are important for defining not only what disease burden the centenarian had, but given her exceptional age, also what she did not have, and how these findings might differ from those of centenarians in other populations.

### CASE REPORT

A 100-year-old woman came to Chubu Hospital in Okinawa, Japan because of shortness of breath. The patient had been healthy until very late in life, when, in short succession, she suffered a T7 compression fracture at age 92

years, two hip fractures at ages 97 and 98 years that were treated with prosthetic replacements, and bronchitis requiring 6 weeks' hospitalization at age 99 years. She had no history of congestive heart failure, myocardial infarction, angina, stroke, hypertension, diabetes, tuberculosis, other pulmonary disease, or cancer. Cognitive impairment was first noted by her daughter and her physician at age 98 years. She did not take any medications. She lived her entire life in Okinawa, where she worked for many years as a farmer. As a young woman, she smoked 2 to 3 cigarettes per day, and she had no history of alcohol use. She used a wheelchair after the second hip fracture and depended on her family for assistance with all activities of daily living.

On presentation, the patient's temperature was 37°C, blood pressure was 130/70 mmHg, pulse was 80/minute, respiratory rate was 24/minute, and her oxygen saturation rate was 78%. A cardiac examination revealed normal sinus rhythm without murmurs. A lung examination was remarkable for coarse crackles at the right base. Her abdomen was soft and not tender, with normal bowel sounds. Pedal edema was noted bilaterally. A blood gas analysis revealed pH, 7.32; partial pressure of carbon dioxide, 79 mmHg; partial pressure of oxygen, 60 mmHg; and bicarbonate, 41 mmHg. Her leukocyte count was 7700 per mm<sup>3</sup> with 81% neutrophils. Her hematocrit concentration was 34%. The patient's blood urea nitrogen and creatinine levels were 22 mg/dl and 0.5 mg/dl, respectively. Her sodium, potassium, chloride,

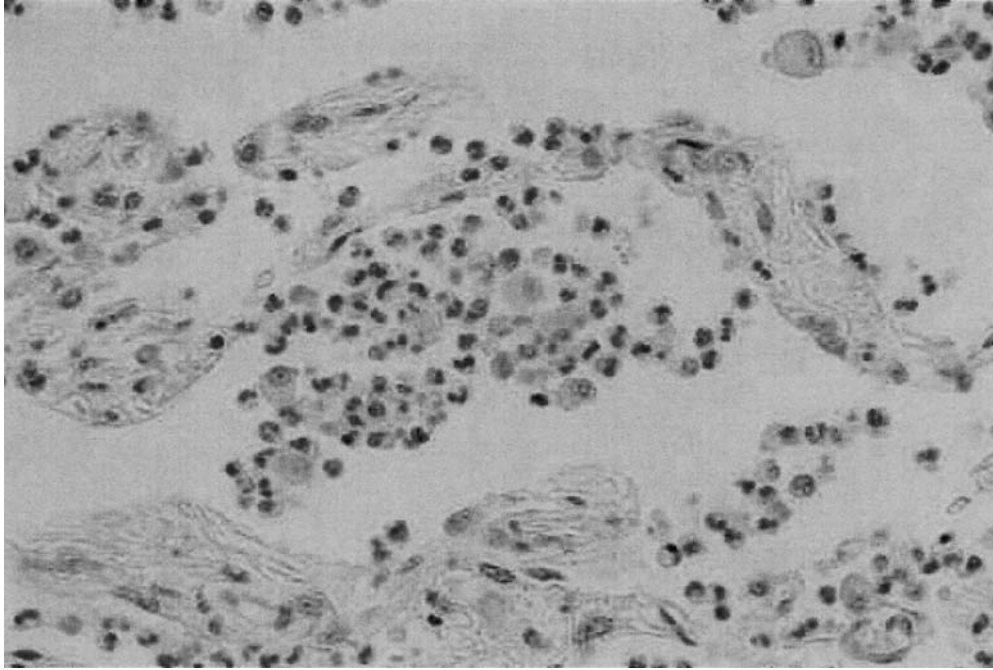


Figure 1. Mild polymorphonuclear leukocyte infiltration of the alveoli (hematoxylin-eosin, original magnification  $\times 400$ ).

and calcium levels were normal. Her total protein level was 5.8 mg/dl and her albumin level was 2.8 mg/dl. A chest radiograph obtained on hospital admission revealed no obvious signs of consolidation or infiltrate. An electrocardiogram was not performed.

The patient was admitted to the hospital and received intravenous fluids and oxygen. Empiric antibiotic therapy was not begun. When sputum cultures grew *Acinobacter baumannii* and *Klebsiella pneumoniae*, ampicillin-sulbactam and cefotaxime were started. The patient improved slowly. After 3 weeks in the hospital on antibiotic therapy, the patient became depressed, expressed thoughts of dying, and refused to eat. Laboratory tests showed a leukocyte count of 7700 per  $\text{mm}^3$ , hematocrit concentration of 22.3%, and blood urea nitrogen and creatinine concentrations of 43 mg/dl and 0.5 mg/dl, respectively. Total protein and albumin concentrations were 3.8 mg/dl and 1.5 mg/dl, respectively. Findings of another chest radiograph were unchanged from those at admission. The patient's family requested that no aggressive measures be taken to prolong the patient's life and that all phlebotomy stop. For the next 2 weeks, the patient remained afebrile, with blood pressure measurements ranging from 70–130/44–64 mmHg; pulse, 64 to 20/minute; respiratory rate, 20 to 30/minute, and oxygen saturation rate, 94% on 3 liters of oxygen. Nearly 6 weeks after admission, the patient suddenly experienced loose bloody stools, her oxygen saturation rate quickly decreased to 60%, and she died.

#### DISCUSSION

The patient's clinical course and autopsy findings indicate that she died of septic bronchopneumonia that resulted from preexisting bronchitis (Figure 1). Malnutrition, cognitive

impairment, immobility, and impaired pulmonary defenses predisposed the patient to the infection and contributed to her decline in health.

Notable autopsy findings (Table 1) include microscopic emphysema possibly secondary to the patient's history of smoking or from "senile lung," an age-associated dilatation of air spaces without loss of elastic tissue, fibrosis, or destruction of the alveolar walls. Microscopic emphysema in smokers and nonsmokers is difficult to distinguish, because both distribute evenly throughout the lung (3). Pulmonary anthracosis, usually seen in city dwellers who inhale carbonaceous matter, was present and may have been due to inhalation of silicon and aluminum during her years of farming (4).

"Normal" age-associated changes of the heart were present, such as lipofuscin deposition, basophilic degeneration, and increased subepicardial fat, but others were notably absent, such as changes in the size of the chambers, mitral valve calcification, and calcification and atherosclerosis of the coronary arteries (5–7). The aorta was severely atherosclerotic but free of age-associated dilatation. That the patient's coronary vessels were free of atherosclerotic narrowing and calcification is remarkable given autopsy reports on white centenarians (those aged 100 to 103 years) and other exceptional survivors (those aged 90 to 103 years), which show coronary vessel narrowing in 66% of patients and coronary calcification in 84% to 97% of patients (5,6). This finding is consistent with the low incidence of and mortality from cardiovascular disease in Okinawa compared with Japan overall and the United States (1,2,8).

The areas of centrilobular necrosis in this patient's liver likely resulted from diminished blood flow just before her death. The low albumin level was likely a result of poor

Table 1. Autopsy Results for Okinawan Centenarian

Organ	Findings
Brain and spinal cord	1. At the request of the family, the brain and spinal cord were not autopsied
Heart	1. 180 grams; Left wall 1 cm thick; right wall 0.3 cm thick 2. Subendocardial fibrosis of left ventricular wall, total heart 99% muscle, 1% fibrosis 3. Subepicardial fat deposition, 2 mm to 5 mm 4. Multiple areas with irregular nuclei and perinuclear lipofuscin deposition 5. Basophilic degeneration in endocardium of left and right ventricles 6. Amyloid deposits sensitive to KMnO <sub>4</sub> in subepicardial interstitial tissue of anterior wall; no amyloid deposits in the intimal layers of the coronary vessels 7. No atrial or ventricular dilatation or enlargement; no areas of infarction; no coronary artery calcification or atherosclerosis; no valvular calcification
Aorta	1. Severe calcified atherosclerosis in ascending and descending aorta 2. Diameter: thoracic aorta, 3 cm; abdominal aorta, 2 cm 3. No dilatation of the ascending or thoracic aorta 4. No amyloid in intimal, medial, or adventitial layers
Paraortic lymph nodes	1. Elevated levels of benign, polyclonal plasma cells
Lungs	1. Weight: left lung, 250 g; right lung, 260 g 2. Pleural membrane intact and without inflammation 3. Upper and lower lobes bilaterally with bronchial inflammation 4. Polymorphonuclear cells and lymphocytes in bronchioles and alveoli 5. Moderate degree of anthracosis in the upper and lower lobes bilaterally 6. Microscopic emphysema in subpleural areas of the upper and lower lobes bilaterally 7. Amyloid deposits sensitive to KMnO <sub>4</sub> scattered throughout the alveolar walls of each lobe bilaterally 8. Amyloid deposits sensitive to KMnO <sub>4</sub> in the intima of the pulmonary artery 9. No lobar consolidation, pleural fluid, or empyema 10. No eosinophils or heart failure cells present
Diaphragm	1. Mild atrophic changes
Kidneys	1. Weight: left kidney, 70 g; right kidney, 50 g 2. Atherosclerosis of the right renal artery 3. Arterioles sclerotic with thickened intima and narrow lumens 4. 10 to 1 ratio of nonischemic to ischemic glomeruli 5. Amyloid deposits sensitive to KMnO <sub>4</sub> in the intimal layers of renal arteries bilaterally 6. Plasma cells scattered in interstitium 7. No loss in total number of glomeruli
Adrenal glands	1. Adrenal glands weighed 4 g each and were unremarkable
Spleen	1. Weight: 45 g 2. Amyloid deposits sensitive to KMnO <sub>4</sub> in intimal layers of splenic artery
Gastrointestinal tract	1. Esophagus normal 2. Gastric mucosal wall 2 mm thick without atrophic gastritis 3. Ileal mucosal wall 1.5 mm thick 4. Hemorrhagic diverticuli 5. No amyloid in walls of the esophagus, stomach, or small or large bowel
Liver	1. Weight: 480 g 2. Diffuse brown atrophy 3. Diffuse ischemic centrilobular necrosis 4. No amyloid deposition
Pancreas	1. Weight: 60 g 2. Amyloid deposits sensitive to KMnO <sub>4</sub> in intimal layers of arterial walls
Gallbladder	1. 8 cm × 3 cm 2. One cholesterol stone 3. Walls with normal thickness and without inflammatory changes
Bladder	1. Bladder wall with normal thickness and without fibrosis 2. Scattered plasma cells in submucosa 3. No amyloid deposition
Uterus and ovaries	1. Mild atrophic changes
Bone	2. L4 vertebra with osteopenia

nutritional intake secondary to dementia and infection, superimposed on the age-associated changes in stomach physiology and hormone and cytokine production that decrease food intake in the elderly (9,10).

This patient escaped atrophic gastritis, a frequent but not inevitable feature of the aging stomach, which leads to reduction in mucosal glandular proliferation (11). Preservation of this patient's gastric mucosa until late in life likely

helped reduce frailty risk, because an intact mucosa with concomitant acid secretion are necessary for absorption of essential minerals such as calcium and iron (12).

The patient's kidneys, like the heart and stomach, appeared remarkably healthy. The usual age-associated changes in kidney structure include loss of 30%–50% of cortical glomeruli by the seventh decade and sclerosis of up to 30% of the remaining glomeruli (13). In this case, 90% of the glomeruli had no sclerosis and there appeared to be no loss in total number.

Amyloid sensitive to potassium permanganate was present in the intima of various arteries, heart interstitium, and alveolar walls. This amyloid was likely a marker of reactive systemic amyloidosis, composed of human amyloid-A protein, not senile systemic amyloidosis, and appeared to be of little clinical significance. The latter is an age-associated deposition of normal transthyretin amyloid in multiple organs but is rarely sensitive to potassium permanganate. Interestingly, amyloid was not found in the intimal layers of the thoracic or abdominal aorta. Intimal amyloid, usually composed of apolipoprotein A-1, may enhance the cytotoxicity of oxidized low-density lipoprotein (14,15). Perhaps the absence of such amyloid in this patient's aorta contributed to her survival despite severe aortic atherosclerosis.

Limited autopsy reports on white centenarians reveal heart disease (coronary artery disease and congestive heart failure) and pneumonia as common causes of death, whereas cancer is infrequent (16,17). In Japan, pneumonia and other infectious diseases account for 40% of centenarian deaths, but coronary heart disease is uncommon (7). The high rates of pneumonia result from a combination of morphologic changes in the lung, chest wall, and respiratory muscles, plus immune function alterations, systemic diseases, and impaired mobility and nutrition (18,19). Heart disease results from age-related loss of cardiomyocytes and conduction tissue and pathologic processes such as hypertension and atherosclerosis (5,6). Low mortality rates from cancer could be ascribed to changes in systemic immune function or to the behavior of tumors in the very old (20).

### Conclusions

The patient's medical history and autopsy findings indicate that she remained remarkably healthy until age 97 years, when, during the next 3 years, she had falls and fractured both hips, had clinically apparent cognitive impairment, became fully dependent in her activities of daily living, and experienced repeated respiratory infections. The delay or escape from many age-associated diseases in this centenarian, particularly coronary heart disease, is consistent with the compression-of-morbidity model (21–23).

Morbidity differences among Okinawan-Japanese, Japanese, and white persons clearly exist, but this autopsy report suggests that such differences continue into even extreme old age. Much of the demographic literature concerning the oldest old supports the notion that at extreme old age, sociodemographic and other determinants of survival have a lesser differential impact on mortality at extreme old age than at younger ages (24). Therefore, further investigation

into population-specific determinants of mortality at extreme old age is therefore merited.

The unique morbidity profile of centenarians and their significant survival advantage likely follows from genetic predisposition, lifestyle choices, and chance, and different pathways may contribute to exceptional survival (22,23,25). Careful premortem and postmortem phenotyping of centenarians is essential to discern the genetic, environmental, and stochastic variants that affect exceptional survival and to determine whether ethnic differences exist in morbidity and mortality rates in very old age.

### ACKNOWLEDGMENTS

Supported by the National Institute on Aging (grants R01AG18721 and R03AG021293-01), Harvard Medical School/Warren-Whitman-Richardson Fellowship, Hebrew Rehabilitation Center for Aged/Men's Associate Research Fellowship, the Ellison Medical Foundation, The Boston University School of Medicine/Miller Family Scholarship, and the Japan Ministry of Health, Labor and Welfare.

Address correspondence to Bradley Willcox, MD, MSc, Pacific Health Research Institute, 846 South Hotel St., Suite 301, Honolulu, HI 96813. E-mail: bjwillcox@phrihawaii.org

### REFERENCES

1. Japan Ministry of Health, Labor and Welfare. Statistics and Information Division. *Japan National Health Statistics for 2000*. Tokyo: Japan Ministry of Health, Labor and Welfare; 2002.
2. World Health Organization. *World Health Report 2000*. Geneva, Switzerland: World Health Organization; 2000.
3. Lamb D, Gillooly M, Farrow ASJ. Microscopic emphysema and its variations with age, smoking and site within the lungs. *Ann NY Acad Sci*. 1991;624:339–340.
4. Ohshima S. Studies on pulmonary anthracosis with special reference to the mineral constitution of intrapulmonary particulate pollutants in the human lung. *Acta Pathol Japan*. 1990;40:41–49.
5. Lie JT, Hammond PI. Pathology of the senescent heart: anatomic observations on 237 autopsy studies of patients 90–105 years old. *Mayo Clinic Proc*. 1988;63:552–564.
6. Roberts WC. The heart at necropsy in centenarians. *Am J Cardiol*. 1998;81:1224–1225.
7. Tauchi H, Sato T, Watanabe T, eds. *Japanese Centenarians: Medical Research for the Final Stages of Human Aging*. Aichi, Japan: Aichi Medical University Press; 1999.
8. Bonita R. Cardiovascular disease in Okinawa. *Lancet*. 1993;341:1185.
9. Morley JE, Thomas DR. Anorexia and aging: pathophysiology. *Nutrition*. 1999;15:499–503.
10. Incalzi RA, Gemma A, Capparella O, Cipriani L, Landi F, Carbonin P. Energy intake and in-hospital starvation: a clinically relevant relationship. *Arch Intern Med*. 1996;156:425–429.
11. Atillasoy E, Holt P. Gastrointestinal proliferation and aging. *J Gerontol A Biol Sci Med Sci*. 1993;48:B43–B49.
12. Steinheber FU. Ageing and the stomach. *Clin Gastroenterol*. 1985;14:657–688.
13. Frocht A, Fillit H. Renal disease in the geriatric patient. *J Am Geriatr Soc*. 1984;32:28–43.
14. Falk R, Comenzo R, Skinner M. The systemic amyloidoses. *N Engl J Med*. 1997;337:898–909.
15. Mucchiano G, Haggqvist B, Sletten K, Westermarck P. Apolipoprotein A-1 derived amyloid in atherosclerotic plaques of the human aorta. *J Pathol*. 2001;193:270–275.
16. John SM, Koelmeyer TD. The forensic pathology of nonagenarians and centenarians: Do they die of old age? (The Auckland experience). *Am J Forensic Med Pathol*. 2001;22:150–154.
17. Saltzstein S, Behling C, Baergen R. Features of cancer in nonagenarians and centenarians. *J Am Geriatr Soc*. 1998;46:994–998.
18. Gyetko M, Towes G. Immunology of the aging lung. *Clin Chest Med*. 1993;14:379–391.

19. Thompson J, Wekstein D, Rhoades J, et al. The immune status of healthy centenarians. *J Am Geriatr Soc.* 1984;32:274–281.
20. Bonafe M, Valensin S, Gianni W, Marigliano V, Franceschi C. The unexpected contribution of immunosenescence to the leveling off of cancer incidence and mortality in the oldest old. *Crit Rev Oncol Hematol.* 2001;39:227–233.
21. Fries J. Aging, natural death, and the compression of morbidity. *N Engl J Med.* 1980;303:130–135.
22. Hitt R, Young-Xu Y, Silver M, Perls T. Centenarians: the older you get, the healthier you have been. *Lancet.* 1999;354:652.
23. Evert J, Lawler E, Bogan H, Perls T. Morbidity profiles of centenarians: survivors, delayers and escapers. *J Gerontol Biol Sci Med Sci.* 2003; 58A:232–237.
24. Elo IT, Preston SH. Educational differentials in mortality: United States, 1979–85. *Soc Sci Med.* 1996;42:47–57.
25. Perls T, Kunkel L, Puca A. The genetics of aging. *Curr Opin Genet Dev.* 2002;12:362–369.

Received July 25, 2003

Accepted September 30, 2003



You can focus on research.

Let NIH repay your student loans.

Realize the potential of your research career.

NIH Loan Repayment Programs pay up to \$35,000 per year of your qualified educational loan debt.

To learn more and apply online, visit [www.lrp.nih.gov](http://www.lrp.nih.gov) or call 1.866.849.4047

**December 15 Deadline**



U.S. Department of Health and Human Services  
National Institutes of Health



**NIH Loan Repayment Programs**