Making Old Age Measure Up

BY JULIE ANN MILLER

Have you not a moist eye, a dry hand, a yellow cheek, a white beard, a decreasing leg, an increasing belly? Is not your voice broken, your wind short, your chin double, your wit single, and every part about you blasted with antiquity?
William Shakespeare,
Henry IV

Everyone knows what it is to be old, so a fountain of youth should not be difficult to recognize. One dip and the wrinkles, aches and tremors all melt away. But in the much slower business of identifying "interventions" that could extend the vigorous and productive years of life, scientists find it no easy task to decide what characteristics provide useful monitors of antiquity. Such markers of aging, however, are necessary if researchers are to find and assess means to slow the rate of aging.

Measures of aging can serve two functions, one more mundane than the other. One tallies the time since a person was born. But such measures are of limited use. As Lewis Carroll's White Queen said, "It's a poor sort of memory that only works backwards." The more exciting, more challenging measure of aging would go forward and reveal how much time, barring disaster, a person has left.

A recent meeting sponsored by the National Institute on Aging discussed a wide variety of characteristics that might provide markers of aging — both the backward- and forward-looking types. The scientists hope to compile a set of appropriate tests that might be used to monitor the aging process. The conference organizers, Edward L. Schneider and Mitchell Reff of the institute, say, "Evidence indicates that aging is probably the cumulative product of multiple basic mechanisms. Since interventions may affect one of these mechanisms, it is crucial that multiple functions be examined."

One potential forward-looking marker described at the meeting is the simple clinical test called vital capacity. It measures the volume of air a person can blow out of the lungs after a deep breath. Using data collected in 30 years of the Framingham study, which includes biennial examinations of 5,200 people, William B. Kannel and Helen Hubert of Boston University School of Medicine report vital capacity can predict both long-term and short-term mortality. They say, "This pulmonary function measurement appears to be an indicator of general health and vigor and literally a measure of living capacity."

The vital capacity falls with age — 9 percent to 27 percent each decade depending on sex and age at the time the test is given. The decline is clear both in cross-sectional data, comparing persons of different ages, and in cohort data, following a group of people as they grow older.

The reason for the decline in vital capacity is not clear. Vital capacity had been thought to reflect how well the lung functions. But Kannel says his data indicate it has more to do with chest size, how well the muscles work and in general how healthy a person is. He suggests an important factor is the ease with which the chest wall can expand and contract.

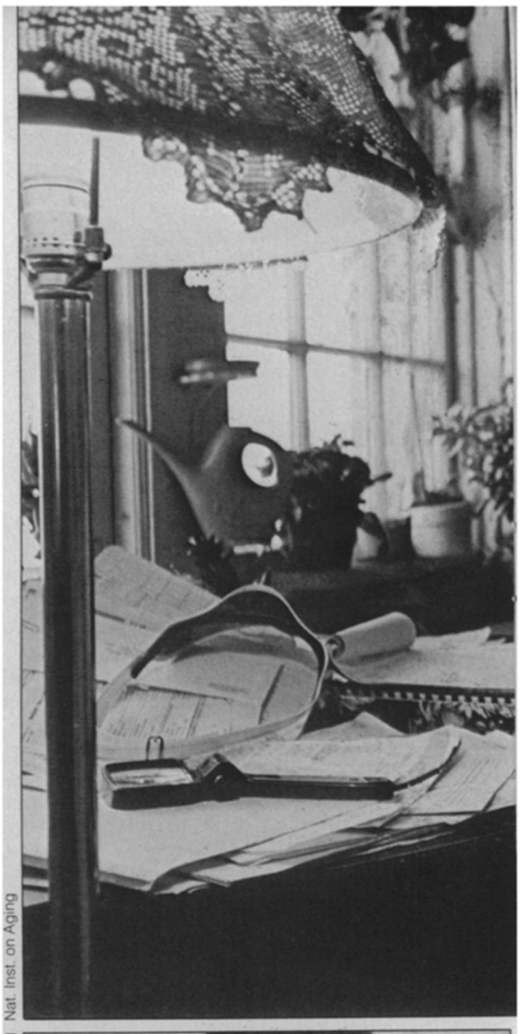
The long-term predictive power of vital capacity is what makes it a good candidate as a marker of aging. Kannel explains that a short-term predictor might only identify someone who is already dying. Of course, sensing such acute physical decline can be useful, and vital capacity also serves that function. "If your vital capacity is declining rapidly, you want to take out lots of life insurance," Kannel says.

But long before a person becomes terminally ill, vital capacity can predict life span. "A person whose vital capacity is always low is not going to do as well as someone whose is always high," Kannel explains. "It can pick out people who are going to die 10 or 20 or 30 years from now." He reports that the vital capacities measured in the first physical exams of the Framingham study were as accurate predictors of mortality over the next 30 years as were more recent exams.

Of all the factors included in the Framingham study, only age was a stronger predictor of death rate. Low vital capacity correlated with excess deaths in both sexes, among both the young and the elderly, among smokers and non-smokers. It was a successful predictor even when the sample excluded people with lung disease, asthma and chest deformities. The association of low vital capacity and excess deaths was independent of obesity and of the factors associated with cardiovascular disease. However, low capacity itself was found to be a high risk factor for cardiovascular disease, as well as for deaths from other causes.

Can a person deliberately alter vital capacity? Kannel says you can certainly make it go down by getting sick or starting to smoke. But so far no one has observed any increase in vital capacity with exercise or physical training. "Improving it seems to be something not too easy to do," Kannel says. But he predicts that the newly discovered correlations with death rates should increase efforts to learn what controls the characteristic and how to manipulate it.

While vital capacity unexpectedly became a prime candidate for monitoring aging, some characteristics traditionally associated with old age were taken off the list. The Framingham data showed no relationship, for example, between life span and graying hair or baldness, even if the



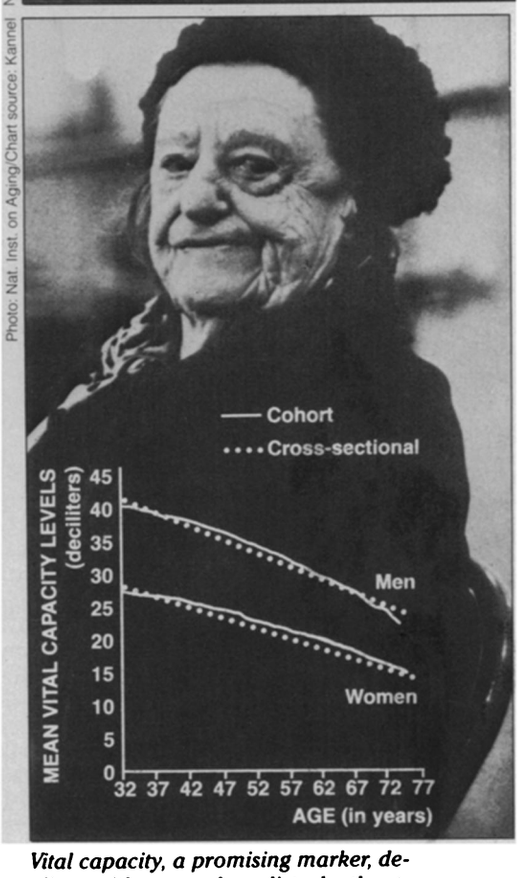
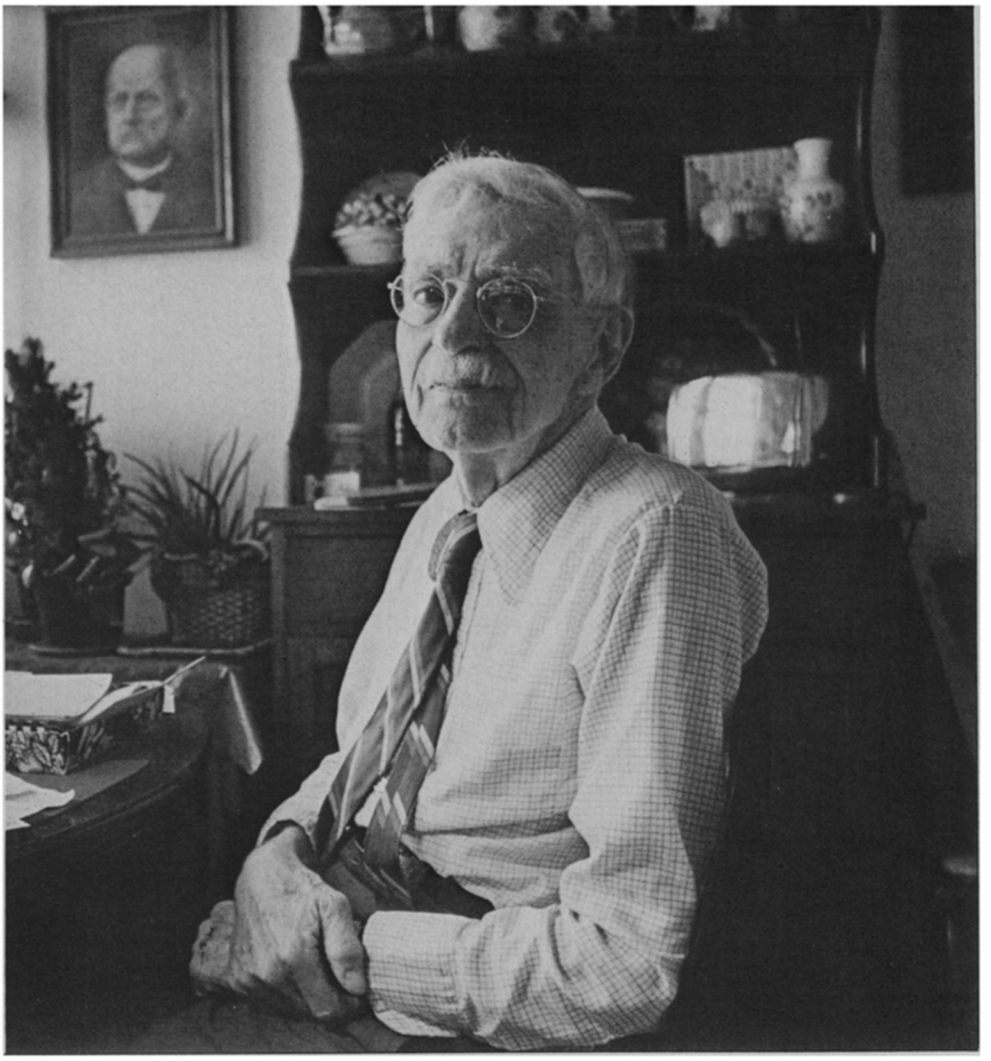
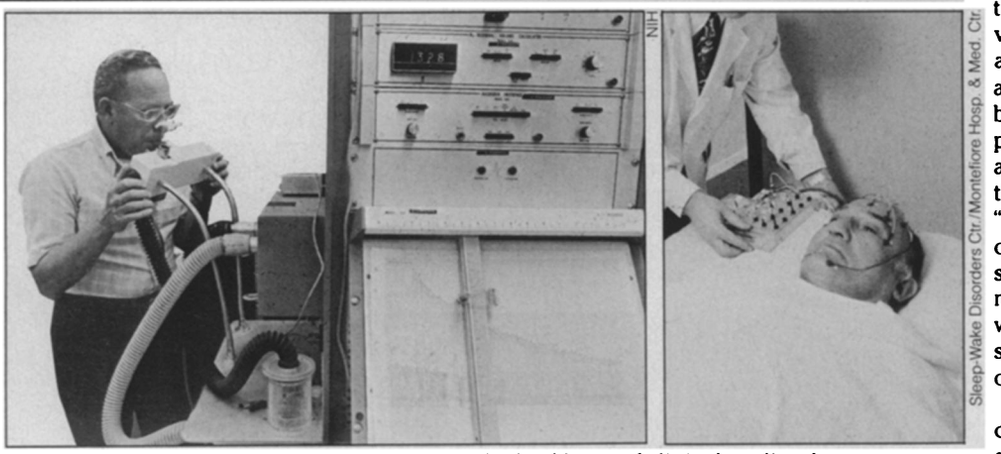


Photo: Nat. Inst. on Aging/Chart source: Kannel Nat. Inst. on Aging

Vital capacity, a promising marker, declines with age and predicts death rate.





Sleep-Wake Disorders Ctr./Montefiore Hosp. & Med. Ctr.

Elderly people in excellent health are the backbone of clinical studies that attempt to distinguish the process of aging from the effects of disease. Subjects undergo vital capacity test (lower left) and sleep monitoring (lower right).

graying or baldness are premature.

Changes in vision and in the eye are other relatively simple clinical observations that may serve as practical measures of aging, suggests Rober Sekuler of Northwestern University in Chicago. "Virtually every one of the eye's many components ages in its own, characteristic way," he says. Pupil size, for example, decreases with age, but the underlying reason for the change is not yet known. In a recent screening of 120 volunteers aged 21 to 81, Sekuler found that all subjects under 55 years of age had pupils at least 4 millimeters in diameter at a set level of illumination, whereas 70 percent of the older subjects had pupils only 3 millimeters across.

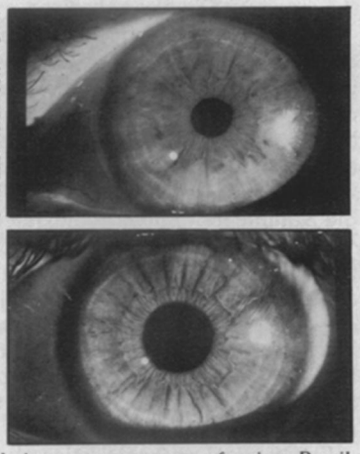
Another vision test measures the amount of contrast that must be provided for a subject to see patterns on a cathode ray tube. Sekuler has found that healthy older volunteers (average age 73) need about twice as much contrast to see a pattern of widely spaced alternating light and dark bars as do young volunteers (average age 18). Tests using faces instead of gratings gave similar results. There was almost no overlap between the groups in the amount of contrast required.

Other characteristics of vision that change with age seem less likely to be useful as markers. Acuity, the ability to resolve fine details, decreases with age, but Sekuler says the distribution is broad enough to allow considerable overlap between groups of 20-year-old and 70-year-old volunteers. Similarly, he rejects the decreasing ability to focus the eyes on near objects as a marker of aging. This ability has reached its lowest level by the age of 60, so it would not be valuable to investigators studying later aging. In addition, Kannel reports that there is no relationship between life span and the inability to focus on near objects.

Biochemical characteristics and sleep parameters also are among the traits being considered as markers of aging. For example, work in several laboratories indicates that human thymic hormone levels fall dramatically after the age of 30, becoming undetectable by the age of 60. A sex hormone called DHEA (dehydroepiandosterone) peaks in early adulthood and then declines dramatically. The significance of that hormone is not known; its absence has not been associated with any disease.

Many elderly persons complain that they do not sleep the way they used to. Sleep time, number of awakenings and breathing disturbances are among the potential markers of aging that can be measured in a sleep laboratory. William C. Dement of Stanford University says that sleep time is shorter, by about 2 hours, and less variable in the elderly. The number of arousals during a night's sleep increases after the age of 40, and even a large number of healthy individuals have breathing problems at night. "The sleeping brain has a harder time managing body functions than does the awake brain," Dement says. "Probably 50 percent of all individuals over the age of 65 have substantial respiratory disturbance during sleep. One may suggest that the respiratory drive, which is vulnerable with the occurrence of sleep, constitutes a physiological marker of an aging process."

One hallmark of aging, previously inaccessible to clinical studies, is the shrunken appearance at autopsy of elderly brains. Now computerized tomography, which provides a detailed display of brain shape by combining X-ray images, has made it possible to view living brains. Marilyn S. Albert of Harvard Medical School described a recent study of 123 normal, healthy volunteers between 23 and 88 years of age. At the Palo Alto Veterans Administration Medical Center, L. M. Zatz, T. L. Jernigan and A. J. Ahumada used a semi-automated computer program to measure the volume of brain tissue and of the ventricles and sulci, the brain's fluid-filled spaces. The fluid volume remained relatively constant (when adjusted for skull size) among the subjects 23 to 60 years old. After 60, the range of values



Retina Lab./Northwestern Univ.

Pupil size as a measure of aging: Pupil of a 79-year-old woman (top) is much smaller than that of a 20-year-old.

became wider and average fluid volumes began to increase. In addition, it appears that the density of the brain tissue falls linearly with age. So far there has been no exploration of whether the observed differences in brain tissue volumes in elderly persons are related to life span.

The decrease in brain tissue volume measured by computerized tomography strikingly parallels age-related cognitive changes, Albert points out. "Measurable cognitive deficits do not occur until individuals are in their early sixties," she says. "It is certainly tempting to speculate that the CT scan and neuropsychological findings are causally, rather than coincidentally, related to one another. If this were the case, CT scan measures of ventricular and sulcal size might be useful markers for functional as well as anatomical aging of the brain."

"These data are clearly very preliminary, the hypotheses based upon them even more so," Albert warns. And the evaluations, cumbersome, expensive and time-consuming, are practical now only as a research tool. Albert suggests, however, that after further investigations a group of selected measurements may be chosen to serve as a more practical measure of age-related changes.

Research on laboratory animals parallels in many areas the clinical investigations on aging. The criteria for a marker of aging are similar, and similarly they have not been completely met by any test. Like clinical tests, an animal measurement should not harm the subject because scientists want to follow an individual animal throughout its life.

Rodents are generally used in research on aging because of their short life spans. Mice and rats are valuable "because they are omnivorous mammals, showing aging patterns similar to those of human beings, but about 30 times faster," says David E. Harrison of Jackson Laboratory in Bar Harbor, Maine. The laboratory maintains aging colonies of healthy mice and rats. The longest-lived subjects survive about 3 years.

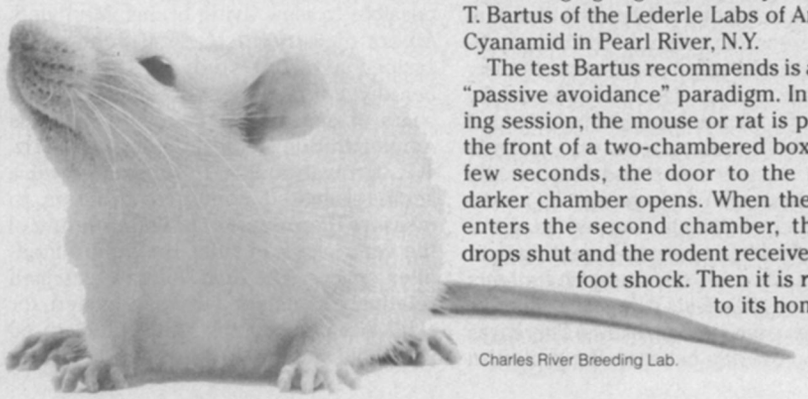
Some tests seem promising both in animals and humans. For example, the reaction of immune system T cells to a foreign substance declines with age. Other tests are limited to animals. Harrison described a simple test that measures the denaturation time of collagen from rodent tail tendons. The older the rodent, the more slowly its collagen denatures in a solution of urea.

Whether the collagen "aging" correlates with subsequent life span is still unclear. Harrison reports that collagen from long-lived mice does not "age" more slowly than that from short-lived mice. In another situation, however, the collagen test is more predictive. Genetically obese mice and normal mice on a restricted diet have approximately the same life span and they survive longer than normal or obese mice eating as they please (fed ad lib). The collagen aging of a food-restricted obese mouse matches that of a restricted-diet normal, even though a normal mouse fed ad lib more closely matches the restricted obese mouse in weight. Harrison says, "Therefore a simple assay of collagen age, when performed as early as 265 days of age, correctly predicted longevities of ad lib fed and restricted obese and normal mice."

A behavioral test also provides an intriguing possibility as a marker of animal aging. "Given the apparent importance of the central nervous system in relation to the organism in general, as well as in aging, it is conceivable that behavioral changes may provide accurate and sensitive information about the physiological state of aging organisms," says Raymond T. Bartus of the Lederle Labs of American Cyanamid in Pearl River, N.Y.

The test Bartus recommends is a simple "passive avoidance" paradigm. In a training session, the mouse or rat is placed in the front of a two-chambered box. After a few seconds, the door to the second, darker chamber opens. When the animal enters the second chamber, the door drops shut and the rodent receives a mild foot shock. Then it is returned to its home cage.

Rodents are convenient models because they age 30 times faster than humans.



Charles River Breeding Lab.

In the test session, hours to weeks later, the animal is again placed in the front chamber. The scientists measure the time it takes for the animal to move through the open door. The longer the mouse or rat hesitates, the greater its "memory" of the previous training session. If animals are tested soon after training, both young and old subjects exhibit similar memory. But if 24 hours elapse between training and testing, younger mice and rats show much greater retention than do older animals. When scientists compared more than a dozen behavioral tasks, the simple passive avoidance test produced the greatest and most reliable deficits with age. Bartus says the deficit seems conceptually and operationally similar to the type of memory loss observed in aged human and non-human primates.

The ideal markers for aging would be traits that when measured at short intervals would reveal the aging rate. Any treatment that might slow aging could then be tested over a period of months instead of requiring literally lifetimes to determine effectiveness.

The treatment now most favorably considered by many scientists as an aging deterrent is restriction of diet. Limiting caloric intake increases the maximum life span in a variety of rodents, and even in the nematode, a parasitic worm. Longer-lived animals still need to be examined. Even in the case of rodents, there is some question whether the process reversed by dietary restriction is truly aging or whether it is simply the adverse effects of severe overindulgence by caged animals eating under normal laboratory conditions.

Other possible interventions that need to be rigorously tested are exercise regimens, anti-oxidant chemicals and specific dietary changes. For instance, Bartus has found that adding choline to the diet of mice can reduce the rate at which their performance in the passive avoidance test declines. The question remains whether it extends their lifespan. So far, clinical work has not demonstrated improved memory among elderly volunteers taking choline (SN: 10/20/79, p. 264).

The spirit at the meeting was optimistic that markers would be found, aging would be measured and interventions eventually analyzed. The goal of extending the period of good health was considered more important than simply extending length of life.

"The potential for assessing human aging is quite promising," says Mark Weksler of Cornell Medical Center in New York. "People are interested in assessing, for its predictive value, where they stand in relation to body age. And they are interested in participating in intervention."

Perhaps scientists are finally on the way to solving the frustrating paradox stated succinctly by Jonathan Swift: "Every man desires to live long, but no man would be old." □