Mortality: Overturning Received Wisdom

New data from flies are undermining the idea that death rates of all species increase automatically with age. Those findings could have consequences even for human beings

Only two things are certain, the old saying goes, death and taxes. And while politicians running for reelection routinely promise cuts in the latter, almost no one is promising to reduce our chances of the former. Indeed, once we reach adulthood our chances of dying appear to rise steadily with every year we live, regardless of who occupies 1600 Pennsylvania Avenue. But is this seemingly inexorable increase in the death rate with advancing age an immutable part of our physiological makeup—a reflection of the fact that there is a biological limit to the human lifespan? Or could advances in health care change that dismal trend? Gerontologists and demographers have argued about those questions for decades—and continue to argue, while policy makers watch for clues about how many aging Americans to expect in years to come so they can plan for such things as Social Security and Medicare.

The scientific underpinning of this debate centers on whether a death rate that rises steadily with age is a universal fact of life in the biological world. Until recently, many researchers in the field of gerontology thought the answer was yes. Now, two papers in this issue of *Science* show that a relentlessly rising death rate does not apply to all species. On page 457, a team headed by James Carey of the University of California (UC), Davis, and James Vaupel, who has a joint appointment at Duke University and Odense University in Denmark, shows that, for at least one species—Mediterranean fruit flies—the risk of death on a given day peaks in old age and then declines. And on page 461, a group headed by James Curtsinger of the University of Minnesota and Vaupel shows a leveling off of the risk of death for 10 different strains of the fruit fly *Drosophila*.

Although there's a huge biological gulf between fruit flies and people, researchers believe these results may change the way the debate over aging and mortality is framed, even for human beings. "I think this is some of the most exciting new work from the point of view of background to human mortality studies," says UC Berkeley demographer Kenneth Wachter. "There has been a raging debate over whether there is a genetically preprogrammed upper limit to lifespan." The fruit fly studies, he says, will "change the way [researchers] talk about these questions."

Until now, most researchers have talked about mortality largely in terms of the "Gompertz law," proposed by British actuary Benjamin Gompertz in 1825, which holds that mortality rates increase exponentially with age. If it is true, the Gompertz law implies that for any species the death rate will climb dramatically in very old age, effectively capping the lifespan. So far, the Gompertz law has seemed to hold for humans, whose chance of death doubles roughly every 8 years during most of adulthood, as well as for all the other species that have been studied by researchers.

Old, older, oldest. But some researchers have argued that the Gompertz law rests on flawed studies of human and animal populations. The critics' chief complaint is that the studies have not included the very old—for example, human beings older than 85 or so—and that the pattern of death at those ages is critical to knowing whether the Gompertz law really applies. "[The] Gompertz [law] itself is not derived from first principles," says Pennsylvania State University demographer James Wood. "Here you have an atheoretical model whose only justification is empirical, but even that justification is not very powerful."

The justification for the Gompertz law began to look very weak indeed when Vaupel and his collaborators in Denmark recently analyzed Scandinavian census information (considered the world's most reliable) for a group of people they call "the oldest old," who are both scarce and subject to poor census data. Their findings suggest that the Gompertz law didn't apply to the very oldest people—their chances of dying didn't continue to increase exponentially (*Science*, 15 November 1991, p. 936).

That was an interesting initial step, but human data have the liability of including countless uncontrolled genetic and environmental variables. So Vaupel and his collaborators took a second approach, using an experimental animal that they could grow in the millions, keep under carefully controlled conditions, and follow precisely enough to record each death.

Carey found an ideal experimental setting in which to do this: an industrial-scale fly-rearing facility in Tapachula, at the southernmost tip of Mexico, that is used to breed billions of medflies, which are then sterilized and released to fight medfly infestations like the one under way in California. Carey set up a project there to rear more than a million medflies and take a census every day, counting each fly that died.

Their surprising conclusion: The likelihood of death peaked at about 15% when the flies were between 40 and 60 days old—a very old age for a fly— then decreased. The most geriatric flies, of 100 days old or older, had only a 4% to 6% chance of dying on any given day—less than they had when they were mere striplings of 20 days.

To those working in a field where the Gompertz rule has long held sway, these are dramatic results. "When you see Carey's paper, it's very impressive," says Minnesota's Curtsinger, whose paper accompanies Carey's in this issue of *Science*. But Curtsinger points out that Carey is working with a mixed population of medflies, containing a variety of genetic types. That variation, he says, could explain the decrease in death rate at the older ages. "If the base population is genetically heterogeneous, and you knock off the wimps early on," says Curtsinger, "then you'd have a more robust population later."

Curtsinger has addressed that question with his own experiments and found that the leveling off of the death rate can't be blamed solely on a class of genetic wimps. He worked with 10 different *Drosophila* populations that are inbred to produce genetically identical individuals. Curtsinger found that genetics

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Swatted. Purebred strains of *Drosophila melanogaster*, like this one, offered James Curtsinger a way to measure the influence of genetic makeup on mortality rates.

did have a definite effect on lifespan—some strains lived twice as long as others—but it clearly wasn't the whole story. As in Carey's mixed population, the death rate among flies of each strain increased until late middle age and then leveled off. Curtsinger concludes that individual risk factors, rather than a genetically programmed rate of decline, are responsible for the deaths of the oldest flies.

The precise factors that are responsible for keeping some flies alive longer than others aren't clear from this work, but "what is absolutely clear," says Curtsinger, "is that we are not seeing a continual exponential increase in the [likelihood of death] at the oldest ages." Vaupel agrees: "Nobody could call [these] Gompertz curves," he says of the death patterns in the two studies. "It's a completely different pattern."

That the new results don't conform to the Gompertz law is undeniable. But not everyone who studies aging agrees on just what the implications of those findings are for the law itself. To evolutionary geneticist Michael Rose of UC Irvine, Gompertz was a straw man to begin with. "I never believed Gompertz for one second," he says. "As evolutionary biologists, we have formal deductive theories rather than the curve-fitting models of demographers like Gompertz." Gompertz only fits a part of the lifespan of humans and animal species that have been studied, Rose adds, comparing the law to fitting a straight line to one part of a curvy curve and ignoring the rest. "A lot of my colleagues do that," he says. "I'm glad that Jim Carey and his co-workers have gone to all this trouble to show these people that their simplified assumptions won't work."

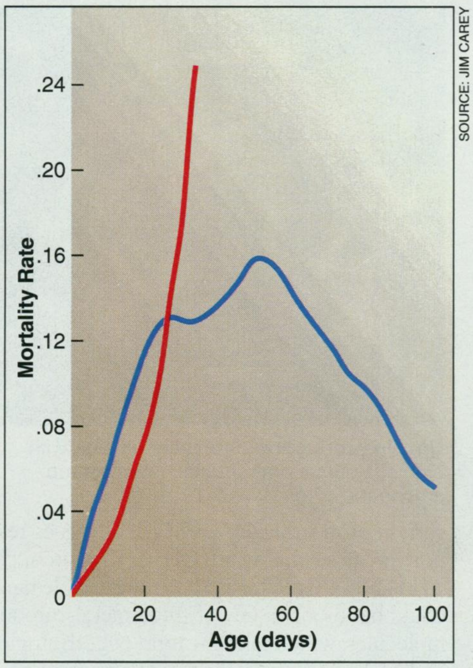
That's one point of view. Another comes from people who aren't willing to give up on Gompertz. Among them is Tom Johnson, who studies aging in nematodes at the University of Colorado. Although Johnson says he is "very convinced by Carey's data," he quickly adds: "Most of the other work I'm familiar with is consistent with [Gompertz] ....It's a definite mistake to say that human populations are like flies more than they are like all of the other systems that do have Gompertzian kinetics." The fruit fly studies, he says, have spurred him to begin a similar large study with nematodes, which, like fruit flies, can be studied in the millions. More experiments like that are needed to test the implications of the fruit fly work, says Berkeley's Wachter: "One experiment doesn't completely swing the field, and it shouldn't. The next species that is looked at might come out the other way."

Whether the new findings have completely swung the field or not, they have certainly challenged the universality of Gompertz's law. And, at the same time, they have begun to cast doubt on some biological theories of aging that were based on that law. "People who have tried to come up with theories of aging have based their theories on the assumption that the mortality rates go up exponentially," says Vaupel. "Those theories are going to have to be rethought."

The simplest version of the biological theories, popularized by gerontologist James Fries, is the notion that the body naturally wears out at age 85 or so, like an old car whose major systems are all failing at once. But that explanation doesn't fit the fruit fly data, nor Vaupel's human data. Vaupel proposes instead that death rates are not driven by an absolute limit to lifespan, but rather that they reflect a collection of causes of death, to which some individuals are more susceptible than others. Like fruit flies, he says, "people are different from each other in terms of their vulnerability to mortality."

Survivor. In Mexico, Jim Carey found a breeding facility for medflies like this one that offered a perfect experimental setup for studying mortality rates.

That range of frailty may be caused by a mixture of genetics and life experience, he adds, but the net result, Vaupel says, is that "the frail tend to die first." After that culling has taken place, he adds, death rates level off for the longest-lived, because they have been selected for hardiness. Carey proposes that, in addition to a weeding-out based on frailty, the risk of death for any given individual may level off with age as well, because, as he puts it, in very old age "the rate of living slows down. Egg laying slows down, the rate of mating slows down, just overall activity slows down, and I think that decreases the overall risk."



Breaking the law. The Gompertz law predicts that mortality of 1.2 million medflies would rise exponentially with age *(red)*. But, in reality, the death rate peaked when the flies were close to 60 days old, then decreased *(blue)*.

The next thing to do, says Wachter, is examine these possibilities biologically. For example, he says, one might search for a biological basis for variations in frailty. "We talk about frailty, or heterogeneity, or hardiness, as a kind of mathematical construct," he says. "It seems to me we have carried that about as far as we can carry it. We need to get more biological information." And that is just what Curtsinger, for one, plans to do. Using inbred fly lines, and DNA markers spaced throughout the fly genome, he plans to map genes that have an influence on frailty or hardiness.

In addition to pointing the way toward biological explanations for aging patterns, the fruit fly work may also change how population biologists view elderly individuals. "It sets up a set of issues you can now address," says Stanford population biologist Marcus Feldman. For example, it raises the question of whether living longer increases a fly's "fitness," in evolutionary terms, as measured by its contribution to the next generation. The geriatric flies may have won the lifespan contest, but do they, over the course of their lives, produce more or healthier offspring than their shorter-lived peers?

Carey hopes that the work will lead population biologists to address not only this kind of question, but also the general issues of how the old contribute to a population. "The old may represent a small proportion of the overall population, but I believe they play a very important role," says Carey. "Old oak trees produce more acorns, older fish produce most of the offspring, and it's the old queen bee that flies away with the swarm." And if researchers can just figure out how the very old manage to get that way—and stay that way—they will provide fodder for medical researchers, health care planners and policy makers, politicians, and people who just want to keep on living.

–Marcia Barinaga