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Fossil shells of the gastropods *Hystrivasma locklini* and *Hystrivasma horridum* from the upper Pliocene Pinecrest Beds (2.0 to 3.5 million years old), Sarasota, Florida. These species are among many that became extinct during the late Pliocene only to be replaced by new species, yielding a biota whose diversity has not changed in 3.5 million years. See page 1626. Other evolutionary events related to the closing of the Isthmus of Panama are discussed on pages 1603, 1624, and 1629. [Photo: Joe Traver; specimens are from the Paleontological Research Institution, Ithaca, NY]

**REPORTS**

Diversity and Extinction of Tropical American Mollusks and Emergence of the Isthmus of Panama
J. B. C. Jackson, P. Jung, A. G. Coates, L. S. Collins

Diversity of Atlantic Coastal Plain Mollusks Since the Pliocene
W. D. Allmon, G. Rosenberg, R. W. Portell, K. S. Schindler

Divergence in Proteins, Mitochondrial DNA, and Reproductive Compatibility Across the Isthmus of Panama

Large Odd-Numbered Carbon Clusters from Fulleren-Ozone Reactions
S. W. McElvany, J. H. Callahan, M. M. Ross, L. D. Lamb, D. R. Huffman

Identification of a Sex Pheromone from a Spider
S. Schulz and S. Toft

Structural Basis of Amino Acid α Helix Propensity
M. Blaber, X. Zhang, B. W. Matthews

A Nonpeptidyl Growth Hormone Secretagogue

Unidirectional Spread of Secondary Sexual Plumage Traits Across an Avian Hybrid Zone
T. J. Parsons, S. L. Olson, M. J. Braun

Evidence of DNA Bending in Transcription Complexes Imaged by Scanning Force Microscopy
W. A. Rees, R. W. Keller, J. P. Vesenka, G. Yang, C. Bustamante

DNA Sequence Determination by Hybridization: A Strategy for Efficient Large-Scale Sequencing

Synthesis of Polycrystalline Chalcopryrite Semiconductors by Microwave Irradiation
C. C. Landry and A. R. Barron

Proliferation of Human Smooth Muscle Cells Promoted by Lipoprotein(a)
D. J. Grainger, H. L. Kirschenlohr, J. C. Metcalfe, P. L. Weisberg, D. P. Wade, R. M. Lawn

Complexes of Ras-GTP with Raf-1 and Mitogen-Activated Protein Kinase Kinase
S. A. Moodie, B. M. Willumsen, M. J. Weber, A. Wolfman

Effects of cAMP Simulate a Late Stage of LTP in Hippocampal CA1 Neurons
U. Frey, Y.-Y. Huang, E. R. Kandel

**TECHNICAL COMMENTS**

Explaining Fruit Fly Longevity

Compositional Interpretations of Medfly Mortality
J. W. Vaupel and J. R. Carey

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Pan-American Science Collaboration

Scientists of the Western Hemisphere have been constructively interacting for decades. Owing to a constellation of changing circumstances, the intensity of collaborative activities is likely to increase. The factors include globalization of industry and concerns about the environment, biodiversity, and the future of planet Earth. Relevant is the revolution in electronic communication that made possible new forms of collaboration. To explore the feasibility of enhanced hemispheric scientific cooperation, the American Association for the Advancement of Science (AAAS) was host on 28 and 29 May to a conference* in which many of the leaders of science in Latin America were participants. Much of the agenda was devoted to descriptions of the state of education and attitude toward scientific research of industry, the public, and politicians. Also provided were inventories of the numbers of scientists and their rates of publication.

World-class scientific research is being conducted in Latin America. However, both the number of scientists and support for them are limited. Together Latin American scientists publish about 1.3% of the world’s scientific literature, and nearly all of the publications originate in Argentina, Brazil, Chile, Mexico, or Venezuela. A larger share might be expected from the more than 300 million inhabitants in the region. Delegates to the conference cited a number of factors to explain the relative paucity of scientific research. One influence is cultural. There has not been status for the kind of knowledge created by the scientific method. Related to this has been a relative absence of industrial research. Thus, the public and politicians could not readily visualize that scientific research in their country could bring national benefits. A consequence of the absence of high technology has been limited gross national products and a lack of funds for research in most of the countries. Insofar as research has been conducted it has taken place at some government-supported facilities, but mainly at universities. Salaries and facilities there are often inadequate. As a result, Latin American scientists seek training or positions in the advanced countries. Those that return to their homelands are especially capable of collaboration with scientists in the institutions where they studied or worked.

The emergence of global competition has not been lost on Latin America. Politicians there have long understood the role of high technology in advancing national incomes and standards of living. But they have lacked an understanding of science and engineering. Often they have behaved as if they assumed that technology was something that came in black boxes. There were many demands that technology be transferred. Those demands were disregarded. Technology is created and best transferred by people. If a country has little or no indigenous scientific and engineering capabilities, it can expect to be out-maneuvered in any purchase of technology. The realities of strong global competition foster changed attitudes toward increasing local capabilities.

While most of the efforts to improve a nation’s economy must be made by its citizens, there are roles for scientists in fostering international science and in turn creating potentials for improvement in living worldwide. Already hundreds of scientists from Canada and the United States have engaged in collaborative research with colleagues in Latin America. For nearly 20 years, the AAAS has had a limited but useful role in interactions with scientific communities of the Western Hemisphere. It has participated in Interciencia and furnished support to the executive secretary of that organization. Interciencia is primarily a nongovernmental organization composed of associations for the advancement of science of 14 countries of the hemisphere. During its existence, Interciencia has sponsored more than 40 symposia on important topics. Annual meetings of the board of directors have included many of the leaders of Latin American science. They have served as nodes for communication to, and identification of, other key scientists in their respective countries.

The AAAS is not a granting agency. But occasionally it has served as a catalyst to channel funds from private foundations and governmental organizations to meritorious scientific activities in Latin America and elsewhere. The recent conference could mark the beginning of enhanced efforts to identify and foster crucial areas for hemispheric collaboration.

Philip H. Abelson
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FRUIT FLY AGING AND MORTALITY

Two reports, "Slowing of mortality rates at older ages in large medfly cohorts" by James R. Carey et al. and "Demography of genotypes: Failure of the limited life-span paradigm in Drosophila melanogaster" by James W. Curtinsinger et al. (16 Oct., pp. 457 and 461, respectively), discuss a phenomenon that was theoretically predicted long ago [see (1) for historical details] to be an inevitable feature of all stochastic models that consider aging as a progressive accumulation of random damage. We recently published the detailed mathematical proof of this prediction (1, pp. 246-276). In short, if destruction of an organism occurs not in one but in two or more sequential random stages, this is sufficient for the phenomenon of aging (mortality increase) to appear and then to vanish at older ages. Each stage of destruction corresponds to one of the organism's vitally important structures being damaged. In the simplest organisms with unique, critical structures, this damage usually leads to their deaths. This is why defects in such organisms do not accumulate and why the organisms themselves do not age. In more complexly structured organisms, where there are many vital structures with significant redundancy, every occurrence of damage does not lead to death. Defects do accumulate, however, giving rise to the phenomenon of aging (mortality increase). Thus, aging is a direct consequence of the increased reliability and life-span of organisms, which in turn result from the redundancy of vital structures. As defects accumulate, the redundancy in the number of key elements finally disappears. As a result, the organism degenerates into a system with no redundancy, that is, a system with elements connected in series, with the result being that any new defect leads to death. In such a state, no further accumulation of damage can be achieved, and the mortality rate levels off.

These explanations were published in our book (1), which was quoted in the reports by Carey et al. and by Curtinsinger et al. in such a way as to possibly leave readers with the mis impression that the book is about limits to the life-span.

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References


The reports by Carey et al. and by Curtinsinger et al. represent a substantive contribution to the study of aging. The premise is simple—mortality rates at extreme old ages have not been reliably estimated because survival to extreme old age has always been a rare event. The solution was to place a huge cohort of a single species in a controlled environment and observe when they died.

These studies revealed non-Gompertzian mortality at older ages for fruit flies, thus indicating that programmed death does not exist. Programmed death is not consistent with evolutionary arguments about senescence (1). Current theories of senescence, based on principles of evolutionary biology, hypothesize that senescence occurs because the force of natural selection declines with age. Consequently, the maintenance and repair mechanisms necessary to ensure reproductive success early in life decline once reproduction begins. So, although we are not genetically programmed to die, neither are we programmed to survive much beyond the ages required to ensure reproductive success.

The Gompertz distribution is an empirical mathematical construct that describes mortality patterns for a genetically heterogeneous population. Once heterogeneity is reduced through differential mortality, a different mathematical function should apply to the surviving subgroup of Methuselahs. Carey's population of medflies was of sufficient size to reveal the heterogeneity not easily quantified in smaller study populations.
It is clear that humans will never acquire the mortality schedule of fruit flies. So, what do these findings imply for humans? One obvious hypothesis is that, as the size of the human population increases, the tail end of the survival distribution will be extended and the number of robust older people will increase. The demographic momentum for population growth will inevitably double or triple the size of the human population over the next half century (10 to 14 billion). As such, we should expect a handful of individuals to survive past the current maximum age of 120. However, an increased number of extremely robust individuals in a larger and more heterogeneous population does not mean that average life expectancy will increase substantially. The Methuselahs of any sexually reproducing species are at the tail end of the survival distribution, where mathematically their numbers cannot influence the summary metric of life expectancy.

Billions of humans have inhabited the Earth during the 100,000 years of our existence as a species, yet we know of no evidence that any human has lived longer than 120 years. Even if "ideal" living conditions had been provided for every human, the frequency of survival past 120 years of age would have been a remote event. The unique genetic characteristics of the handful of robust individuals who survive into extreme old age are just that—unique. The rest of the population cannot expect to be as physiologically robust and resistant to disease as these few.

From the studies of Carey et al. and Curtsinger et al., some might come to the erroneous conclusion that they need only survive the rest of the population past the first 100 years or so, after which their mortality rates would level off. We believe that with continuing reductions in mortality at older ages (driven by life-style changes and advances in medical technology), future survivors to extreme old age will be more heterogeneous than ever before. The same genetic variability that permits morphological diversity, and thus evolution, will not also allow for a homogeneous population that contains only Methuselahs.

There is no denying the importance of and interest in these studies—they have permitted the reliable estimation of old age mortality for a single species for the first time. Their findings do not contribute, however, to predictions of upper limits of life expectancy for a human population. The only way life expectancy at birth could increase beyond about 85 years would be to find some way for death rates to decline dramatically below the already low levels observed today in countries with low mortality, which would be a difficult task at best (2). Gains in human life expectancy are likely to be small even with anticipated breakthroughs in molecular biology that could modify some of the inevitable failure of maintenance and repair mechanisms.

The research of Carey et al. and Curtsinger et al. reminds us that there are indeed Methuselahs living among every heterogeneous population, and their numbers are expected to grow with increasing population size. As has always been the case, however, the Methuselahs will have a negligible effect on the summary metric of life expectancy, and this applies to fruit flies and humans alike.

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Carey et al. found a declining age-specific mortality rate at advanced ages, which contrasts with conventional models of demography, particularly that of Gompertz (1). The results of Carey et al. may arise from an ecological dependence of fly mortality rate on population density, not because of some undiscovered property of extremely old flies.

In experiment 3 of figure 2 of the report by Carey et al. (p. 458), the age-specific mortality rate rose steadily for 60 days, after which it fell until about day 100. The survival data from their table 1 show 1.2 million flies at the start of the experiment, but only 1204 flies at day 64. Unless the volume of the fly cages was reduced by a factor of 1000, the population density of the flies fell dramatically.

Studies of the effect of population density on longevity (2) reveal that longevity falls dramatically with population density in Drosophila melanogaster. When high concentrations of flies were handled without replacement, a dramatic increase in age-specific mortality rate with age, followed by a fall, was observed.

If the mortality rates arising from the different handling methods of Carey et al. are compared, it is apparent that the large-cage populations have a general elevation in age-specific mortality. In experiments 1 and 2 of Carey et al. there were lower handling densities, and these flies exhibited lower age-specific mortality rates than flies from cages, at least until densities within cages fell substantially, that is, at later ages. In addition, the data from their experiment 1, in which flies were handled individually, generally indicate a rising age-specific mortality rate, quite unlike the data from the population cage experiment with 1.2 million flies.

While we do not wish to defend the Gompertz model, which has undoubtedly been "successfully" applied to other problematic data, in our view, the findings of Carey et al. indicate that complex crowding affected the experiments and that these effects could have given rise to deviations from a Gompertz model for reasons that have little to do with the biology of aging.

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References

Response: Other explanations exist for the leveling off of mortality at advanced ages besides the one described by Gavrilov and Gavriloiva, two of which were included in our reports (1, 2)—cohort heterogeneity and changes at the individual level. Furthermore, available evidence does not conclusively demonstrate that death rates for all species necessarily approach a constant level at advanced ages. Our findings, taken together with human data, simply suggest that death rates among the very oldest may not increase exponentially, at least in some species. It is possible that mortality patterns at advanced ages differ across species and result from complicated interaction of mortality selection, debilitation, recuperation, and acquired resistance (3).

We did not cite the entire book by Gavrilov and Gavriloiva as one on life-span limits; rather we cited a specific page in their book (4, p. 128), where a framework...
for testing the hypotheses for the existence of life-span limits can be found.

Olshansky et al. state that death rates have to fall substantially if human life expectancy is to increase beyond age 85. This is correct. Their view that this is unlikely is debatable. If death rates decline steadily at a rate of 2% per year, then they will fall to about half of current levels within three or four decades and to about a quarter of current levels within seven or eight decades, that is, within the lifetimes of children alive today. Given such progress, the average newborn girl in the United States would live 100 years (5). It may seem "difficult" to cut mortality by a factor of four, but continued reductions at a rate of 1, 2, or 3% per year are not implausible. Prolonged but gradual progress might be achieved even without "breakthroughs in molecular biology" through our gradual understanding of salubrious nutrition and behavior, "successful aging," and disease and disability processes and through prevention or postponement of illnesses as well as treatment and cure (6).

Olshansky et al. assert that only individuals with "unique genetic characteristics ... survive into extreme old age ...." Although genetic factors influence longevity, human nonagenarians and centenarians are genetically heterogeneous (7), and most of the genotypes in our Drosophila experiments included long-lived individuals (2). Because "ideal' living conditions" are not yet well understood and centenarians up until now have lived most of their lives under far from ideal conditions, how many humans can survive past age 120 if they live under ideal conditions all their lives is an open question.

Medflies and Drosophila start reproducing within 3 days of emergence and have life expectancies in the wild of a week or two. Olshansky et al. say that individuals are not "programmed to survive much beyond the ages required to ensure reproductive success." Some medflies in our experiments, however, survived more than 200 days, and some Drosophila more than 100 days. Olshansky et al. contend that in a population with little genetic heterogeneity, a mortality function other than the Gompertz "should apply." They present no evidence or theoretical justification, do not describe the nature of the function, and do not mention our research on the mortality of genetically homogeneous populations of Drosophila (2) and on the relationship between the mortality patterns of populations and more homogeneous subpopulations (8).

The remark by Olshansky et al. that there are Methuselahs in every population misses the significance of our findings about medflies and Drosophila. In sharp contrast to human experience, the age trajectory of mortality did not approach one, but roughly leveled off at a modest point. There were true Methuselahs among the flies—individuals whose life-span in comparison with the typical fly was analogous to Methuselah's life-span of 969 years. Thus the pattern of mortality among the flies we studied was fundamentally different from the observed pattern in at least modern human populations.

We do not dispute the findings of previous studies including those cited by Nusbaum and his colleagues showing that, in general, life expectancy at maturation is inversely related to initial cohort density (9, 10). Rather, we view the relationship as irrelevant to our conclusion that mortality rates slow at older ages. This is because most studies of cohort density have shown that initial densities influence mortality rates far more at young ages than at old ages, when mortality has much less influence on initial life expectancy (11). The mortality decline in our 1.2 million medfly experiment began at day 60, when an average of only 16 flies per cage were alive, and continued until day 100, when an average of only one to two flies per cage were alive. Although changes in density at such low levels of crowding are unlikely to
explain the mortality decline, we are conducting further experiments and analyses of density effects. So far we have found no statistical evidence in the data for 1.2 million medflies maintained in 167 separate cages that slowing of mortality rates at older ages was an artifact of decreasing cage population densities. The evidence included correlation coefficients for cage population densities at three ages (10, 30, and 45 days) plotted against the respective age-specific life expectancies and mortality rates. In all cases the sign of the regression equation slope was opposite that predicted by density effects, and correlation coefficients were small. Furthermore, density effects alone cannot explain the slowing of mortality at older ages in our two medfly experiments in which flies were maintained in solitary confinement.

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References and Notes

11. For example, the study by Pearl, Miner, and Parker (9) showed that mortality rates in Drosophila cohorts with initial densities ranging from 2 to 200 flies per bottle were essentially independent of initial density at ages 50 days and older.

Corrections and Clarifications

The names of Charles Kennel and Thomas A. Tombrello, Jr., were misspelled in John Travis' 30 April News & Comment article "LIGO: A $250 million gamble" (p. 612).
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<thead>
<tr>
<th>RECEPTOR</th>
<th>SUBTYPE</th>
<th>CATALOGUE #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>D1 (human)</td>
<td>BSR-D1H</td>
</tr>
<tr>
<td></td>
<td>D2 (human)</td>
<td>BSR-D2H</td>
</tr>
<tr>
<td></td>
<td>D3 (rat)</td>
<td>BSR-D3R</td>
</tr>
<tr>
<td></td>
<td>D5 (human)</td>
<td>BSR-D5H</td>
</tr>
<tr>
<td>Muscarinic</td>
<td>M1 (human)</td>
<td>BSR-M1H</td>
</tr>
<tr>
<td></td>
<td>M2 (human)</td>
<td>BSR-M2H</td>
</tr>
<tr>
<td></td>
<td>M3 (human)</td>
<td>BSR-M3H</td>
</tr>
<tr>
<td></td>
<td>M4 (human)</td>
<td>BSR-M4H</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Current FBS Requirements</th>
<th>FBS Cost ($320/L*)</th>
<th>% Switch to FETALCLONE®</th>
<th>Total Cost of Using FETALCLONE® &amp; FBS</th>
<th>COST SAVINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Liters</td>
<td>$16,000</td>
<td>10%</td>
<td>$15,200</td>
<td>$800</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30%</td>
<td>$13,600</td>
<td>$2,400</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50%</td>
<td>$12,000</td>
<td>$4,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70%</td>
<td>$10,400</td>
<td>$5,600</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90%</td>
<td>$8,800</td>
<td>$7,200</td>
</tr>
</tbody>
</table>

*Hypothetical pricing based on current FBS market prices only. Not to be interpreted as actual price.

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