What determines age-related disease: do we know all the right questions?

David A. Juckett

Received: 20 August 2009 / Accepted: 21 October 2009 / Published online: 11 November 2009
© American Aging Association 2009

Abstract The average human lifespan has increased throughout the last century due to the mitigation of many infectious diseases. More people now die of age-related diseases than ever before, but these diseases have been resistant to elimination. Progress has been made in treatments and preventative measures to delay the onsets of these diseases, but most cancers and vascular diseases are still with us and they kill about the same fraction of the population year after year. For example, US Caucasian female deaths from breast plus genital cancers have remained a fairly constant ~7% of the age-related disease deaths from 1938 to 1998 and have been consistently ~2-fold greater than female colon plus rectal cancer deaths over that span. This type of stability pattern pervades the age-related diseases and suggests that intrinsic properties within populations determine these fractions. Recognizing this pattern and deciphering its origin will be necessary for the complete understanding of these major causes of death. It would appear that more than the random processes of aging drive this effect. The question is how to meaningfully

approach this problem. This commentary discusses the epidemiological and aging perspectives and their current limitations in providing an explanation. The age of bioinformatics offers hope, but only if creative systems approaches are forthcoming.

Keywords Disease · Aging · Epidemiology · Bioinformatics · Genetics · Failure mechanisms

There are many theories and discussions addressing the origins of human disease (e.g., Strehler 1977; Finch 1990; Gavrilov and Gavrilova 1991, 2002; Carnes et al. 2006, 2008; Mackenbach 2006; Ozanne and Constancia 2007). It is well documented that diseases can occur from obvious extrinsic insults such as infections, nutrient deficiencies, environmental molecules (e.g., poisons), environmental energy fluxes (e.g., radiation), and traumas that place organs or systems out of balance. Diseases can also occur from a variety of intrinsic sources that lead to imbalances in the organism's system dynamics. Alterations in the system's information database (genetic and epigenetic changes) or in the complex feedback loops governing homeostasis can lead to autoimmune disorders, neoplasia, vascular diseases, or isolated organ malfunctions (Mackenbach 2006). Some of these intrinsic imbalances can be traced back to extrinsic sources, others to inherited misinformation, and others to random mutations that might be considered the price of operating in a thermal

D. A. Juckett (✉)
Barros Research Institute,
2430 College Rd,
Holt, MI 48842, USA
e-mail: juckett@msu.edu

D. A. Juckett
Department of Chemistry, Michigan State University,
East Lansing, MI 48824, USA

environment. Most of the diseases of intrinsic origin and many of those of extrinsic origin increase in frequency as an individual ages. This has naturally led investigators to begin identifying the environmental effects and spontaneous mutations in aging populations in an attempt to understand the mechanistic origins of the major age-related diseases. So far, this has led to a considerable accumulation of information but only limited intervention success.

One can classify diseases into those that currently can be manipulated and those that cannot. In many cases, this is a distinction between diseases with extrinsic sources and those with intrinsic sources linked in some way to senescence (Carnes et al. 2008). It is clear in Fig. 1a, the outcomes of some diseases can be greatly altered by intervention. In the case of some infectious diseases, like tuberculosis or syphilis, treatments have reduced deaths by 100–1,000-fold over 60 years. Highlighting the opposite trend is the case of lung cancer, where self-induced environmental toxin exposures greatly increase disease prevalence and death. The vast majority of the population, however, die of diseases that have been largely unaffected by modern medicine or changes in the environment. Examples are shown in Fig. 1b, where the fractions of total deaths, summed over all ages, are plotted over time. The stability of this pattern is strikingly different than the changes seen in Fig. 1a because it indicates these diseases are difficult to manipulate. Presenting the data in this fashion reveals a pattern often hidden by standard analyses, in which disease rates are calculated or survivorship curves are examined. For example, rate calculations inherently show decreases if the deaths are pushed out to higher ages (Kort et al. 2009). These rates are often highlighted as evidence for winning the war against disease, but in actuality, it is a skewed interpretation of the facts. As shown in Fig. 1b, people eventually die of diseases according to a population-specific pattern.

All of the known origin-of-disease theories have not specifically addressed this fundamental stability observation even though the intractability of the intrinsic diseases of aging was recognized by Gompertz and Makeham in the nineteenth century. The long-term stability for the occurrence of each disease not only indicates our inability to eradicate these diseases but also more importantly indicates that intrinsic features of the population probably

govern disease incidence and ultimate death. This stability of the relative ratios between diseases, first pointed out by Juckett and Rosenberg (1991) seem unaffected by stochastic forces, changes in pollution levels, differences in cohorts and their lifestyles, or increases in median lifespans. These intrinsic characteristics are likely intertwined with aging processes, but the nature of this interaction is an important mystery that needs to be addressed.

It is also worthwhile to highlight another important attribute of disease subclasses. In cancer, some cancer rates decrease in the population while others increase, creating a fairly obvious compensation effect among subsets (Fig. 2a). Since the percent change in total cancer rates (all sites) is quite small over five decades, one must conclude that there exists a stable portion of the total population that is prone to cancer. A byproduct of this effect is that individuals cured of one cancer may still be prone to cancers in other organs, which implicates an organism-wide susceptibility to the transformations leading to cancer. This suggests that there is a common mechanism that can be understood and possibly manipulated.

While modern medicine has not eradicated most age-related disease, it has increased the median lifespan, reduced morbidity, and enhanced the quality of life for many of the disease subpopulations (Kort et al. 2009). This can be seen in Fig. 2b for the same cancers depicted in Fig. 2a. In each case, there is a substantive increase in the 5-year survival for these diseases within the last decade compared to the 1955–1959 era. This has occurred through advances in prevention, early detection, and improved treatments. This success has reduced the cancer “rate,” but since these strategies have failed to eliminate cancers, it implies that our knowledge of how and why these diseases develop remains inadequate at the most fundamental level.

Exploring the stability phenomenon of Fig. 1b is tantamount to exploring the origin of diseases. It is this author’s contention that this exploration must begin by peeling away the aging processes and the environmental risk processes to reveal the underlying structure that pervades all members of the population (species). Two approaches to disease and death analysis have been in place for decades. These are embodied by the separate disciplines of epidemiology and aging research. Each has accumulated significant insights into the modulators of disease and dying but

Fig. 1 Total Caucasian female deaths as a fraction of all age-related deaths in a given year (US Department of Health and Human Services, 1939). Age-related deaths consist of total deaths minus those from infections, early infancy, complications of pregnancy, violence, and poisonings.

a Disease deaths that have varied significantly over the recent decades. For syphilis and tuberculosis, the denominator also includes infectious diseases.

b Examples of disease deaths that have remained predominantly stable. Plotted on the same scale as (a) for ease in comparison

neither has elaborated this underlying structure upon which these modulators act.

The epidemiological perspective explores diseases by identifying and grading the various risk factors, population properties, and temporal relationships that perturb the occurrence of a given disease. This can often explain the variations that occur in the number of people afflicted with a specific condition, at a specific time and location, and at a specific age. The underlying assumption is that the risk factors associated with the variation of disease incidence are also the same factors that lead to the disease itself. While this approach works well in infectious disease, it does not necessarily follow for age-related diseases.

The second perspective on the origin of the age-related diseases is the aging perspective, which is composed of both degradative theories (Strehler 1977) and evolutionary theories (Finch 1990; Gavrilov and Gavrilova 2002). The reasons why multicellular organisms age is continually debated, but the fact that aging is universally observed is not in doubt. Several mechanisms have been proposed to explain the aging phenomenon, and they are also pertinent to consider for the origin of diseases. These mechanisms include the general inability to fight entropy; mutations that specifically favor the survival of the species over the survival of the individual; mutations that favor the reproductive years and are accidentally detrimental to

Fig. 2 Changes in cancer mortality (SEER Cancer Statistics Review 1975). **a** Percent changes in the average age-specific mortality rates for various cancers between 1950 and 2005. **b** Percent increase in 5-year survival after diagnosis, between the 1955–1959 era and the 1996–2004 era, for the same diseases listed in panel **a**

the post-reproductive years; or passive accumulation of defects that are unaffected by selective pressures because they have no impact on species survival but are antagonistic to long-term homeostasis and longevity of the individual.

The implicit assumption in the aging perspective is that age-related diseases are, in fact, age induced. This perspective posits that age-related diseases depend primarily on the progressive accumulation of random damage rather than on specific risks. This damage is tempered by the genetic background and is assumed to be irreversible because the selective pressures have not existed to generate repair mechanisms capable of eliminating all damage. The accumulation of damage within individual organs or systems leads to failures that are unique to these structures. The many risk factors for each disease simply perturb the rate at which this process occurs.

Intuitively, this would seem to imply that the stable fractions of disease deaths are operational failures related to the intrinsic susceptibility of each organ or system to the continual degradative pressures, where these susceptibilities, in turn, result from the species' genetics. Just as in engineering, failures depend on the overall system design (architecture), the rules specific to the type of failure (degradative mechanisms), the wear and tear profile (use), the passage of time, and chance. In the case of complex biosystems, the overall architecture is certainly the result of a long-term evolutionary trajectory but may also be under short-term selective pressure (e.g., epigenetic changes during development) (Ozanne and Constancia 2007). The wear and tear profile over the course of time determines such degradations as loss of information (genetic and epigenetic mutations during the life course), loss of structural integrity (increases in entropy), and breakdowns in the emergent property of complexity (multisystem failure). Failures occurring at the cellular, organ, or system level would then lead to such conditions as neoplasia, arrhythmias, or vascular disease, respectively. The “rules specific to the type of failure,” however, would be critical for the complete understanding of the differences between disease states. Therefore, knowledge of the static design, the dynamic operations, and the behavior under stressed conditions (extreme values) would all be necessary for deducing the causes of diseases and their relative prevalences.

The challenge is how to obtain this information. Can we deduce it from epidemiological studies? Risk

factor analysis can help define the architecture (genetics) or the factors influencing the rates of wear and tear (exposures and lifestyles) occurring from environmental factors, genetic predispositions, developmental modulations, and accumulated mutations. This can add important insights and help understand the dynamics under stressed conditions. Such analyses, however, are probably not sufficient to reach the final goal because they focus on the responses between different risk groups. In the worst-case scenario, where the differences only represent variations in the rate of wear and tear along a hidden pathway, the crucial information on the pathway itself (rules of failure) may not be obtainable. The goal of these epidemiological studies will have to be the determination of what is common among subgroups of a disease, in addition to what is different.

Can aging studies supply the answers? Most experimental aging studies are performed in other species under highly controlled conditions. Often, the goal is to study what alters the rate of aging, which has the same problem as the epidemiological studies that only detect the changes in the rates of disease occurrence. Furthermore, many aging studies do not explore the constellation of diseases that may be affecting the longevity of the test species. In *Drosophila* and *Caenorhabditis elegans*, for example, the “diseases of aging” may not even be well known. Therefore, the architecture in which the damage is accumulating is poorly defined. However, considerable progress has been made at the cellular level related to genetic degradation, altered gene expression, mitochondrial dysfunction, and metabolism variations (e.g., Finch 1990; Burton 2009). One can assume that this information will be valuable for understanding the complexities emerging from the slowly degrading networks of biochemical pathways that make up the total architecture and rules of failure for each disease.

In that vein, it is tempting for the immediate future to simply rely on deciphering the patterns in personalized human genome databases and on the future accumulation of epigenomic, transcriptomic, proteomic, and metabolomic data (Kandpal et al. 2009) to provide the details of the human architecture. But this information will arrive with tsunami force and without interpretation. Hoping that current bioinformatic software will organize it into meaningful constructs may be asking for too much. This information, which is fundamen-

tally cellular information, must be understood in a more integrated context. Along these lines, system-level approaches are beginning to reappear (e.g., Lerner 2007) after the reductionist interlude of genome sequencing has begun to play out, but these approaches cannot be pulled from thin air. While these new approaches are receiving more attention and various methodologies are suitable for the study of evolution, development, and aging, there must be a vision to guide them—organizational constructs that are meaningful to both aging and disease. These system-level approaches must account for the forces that operate in an aging organism while identifying the factors that define which failure paths will be followed. The context of Fig. 1b suggests that specific failure paths operating in specific architectures are fundamental to the evolutionary heritage of the species and once discovered will be seminal to the effective treatment of the underlying causes of disease.

Paraphrasing Carl Sagan from his *Cosmos* series, biology (life) is more like history than physics or chemistry, in that it is a product of past events. Current snapshots that catalog components and pathways in a biological system will help us understand the physics and chemistry on which life depends, but they will not contain the necessary information to understand life itself, its variations, and its malfunctions. Ultimately, the history contained within the Earth's collective genome must be unraveled, and here, the bioinformatics revolution will have to lead the way. But, only by developing the ontological relationships (Pesquita et al. 2009) in addition to taxonomies will this be possible. These ontological relationships must combine with system science approaches and creative hypotheses to decipher the various disease mysteries because Fig. 1b would imply that diseases are more than random failures; they are part of the history maintained in the collective genome. The hypotheses that will be needed for this approach must soar above many of the bread-and-butter hypotheses that dominate current epidemiology and aging research. Considering the lack of awareness and discussion of the phenomenon highlighted by Fig. 1b and previously in Juckett and Rosenberg (1991), perhaps this commentary will inspire investigators within the fields of aging and epidemiology, who focus on the intrinsic causes of

diseases, to join with the investigators of bioinformatics to expand the theoretical scaffolding necessary to organize the new universe of bio-information.

Acknowledgements This work was supported by the Barros Research Institute and by a joint operating agreement grant from the Michigan State University Foundation. I appreciate valuable discussions over the years with Bernie Strehler, Barney Rosenberg (both deceased) and Leonid Gavrilov.

References

- Burton DGA (2009) Cellular senescence, ageing and disease. *AGE* 31:1–9
- Carnes BA, Holden LR, Olshansky SJ, Witten TM, Siegel JS (2006) Mortality partitions and their relevance to research on senescence. *Biogerontology* 7:183–198
- Carnes BA, Staats DO, Sonntag WE (2008) Does senescence give rise to disease? *Mech Ageing Dev* 129:693–699
- Finch CE (1990) Longevity, senescence, and the genome. University of Chicago Press, Chicago
- Gavrilov LA, Gavrilova NS (1991) The biology of life span: a quantitative approach. Harwood, London
- Gavrilov LA, Gavrilova NS (2002) Evolutionary theories of aging and longevity. *ScientificWorldJournal* 2:339–356
- Juckett DA, Rosenberg B (1991) An unexpected periodicity among the prevalences of human age-related, mortal diseases. *Mech Ageing Dev* 59:139–152
- Kandpal RP, Saviola B, Felton J (2009) The era of 'omics unlimited. *BioTechniques* 46:351–355
- Kort EJ, Paneth N, Woude GFV (2009) The decline in U.S. cancer mortality in people born since 1925. *Cancer Res* 69:6500–6505
- Lerner VS (2007) Systems science, information systems theory, and informational macrodynamics: review. *Kibernetes* 36:192–224
- Mackenbach JP (2006) The origins of human disease: a short story on “where diseases come from”. *J Epidemiol Community Health* 60:81–86
- Ozanne SE, Constanica M (2007) Mechanisms of disease: the developmental origins of disease and the role of the epigenotype. *Nat Clin Pract Endocrinol Metab* 3:539–546
- Pesquita C, Faria D, Falcão AO, Lord P, Couto FM (2009) Semantic Similarity in Biomedical Ontologies. *PLoS Comput Biol* 5:e1000443. doi:10.1371/journal.pcbi.1000443
- Strehler BL (1977) Time, cells, and aging. Academic, New York
- SEER Cancer Statistics Review 1975–2005, Table I-3, Summary of changes in cancer mortality, 1950–2005 and 5-year relative survival rates, 1950–2004. National Cancer Institutes, US National Institutes of Health.
- US Department of Health and Human Services, Vital Statistics of the United States 1939–1998, National Center for Health Statistics. Government Printing Office, Washington, D.C.