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Commentary: Ageing—what's all the noise about? Developments after Gärtner

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It would be possible but mistaken to presuppose a message of regret in Gärtner's[1] account of 'the limited success of a 30 year long effort to standardize laboratory animals'. Thirty years is three-quarters of the typical career and the outcome might seem like failure. However, in the spirit of Isaac Asimov's oft-quoted remark 'The most exciting phrase to hear in science, the one that heralds new discoveries, is not ''Eureka!'' (I've found it!), but ''That's funny . . .'' ', the report of 'a third component causing random variability beside environment and genotype' was an exciting milestone. For Caleb Finch and me, coming across Gärtner's paper during the final stages of writing our book *Chance, Development and Ageing*[2] was welcome confirmation that someone before us was thinking along similar lines. In our case, we were interested in the extensive stochastic variation manifest in ageing, which seems not to be explicable in terms of the usual dichotomy between genes and environment. The commonplace dismissal that everything which is not 'genetic' should be counted as 'environmental' makes little sense when confronted with the fact that within an isogenic population of nematode worms (*Caenorhabditis elegans*) raised in extremely uniform conditions (even to the extent of stirred liquid cultures), individuals show enormous variation in lifespan. This variation is all the more striking because the worms' development is so exceptionally reproducible, each worm reaching adulthood in uniform time and with exactly 959 somatic cells. Of course, genes can alter worm lifespan, as does environment (e.g. temperature), but the variance in populations of extended-lifespan mutants and wild-type worms was such that the lifespan distributions showed extensive overlap in spite of a large difference in mean.[3]

Since Gärtner's publication, much has been learnt about the noise that operates at all levels within the organisms. Phelan and Austad[4] confirmed that often in laboratory studies of animal models of ageing, inbred strains exhibit less uniformity than F_1 hybrids. Random variability affects how molecules diffuse and interact, how cell numbers in different organs vary through random effects on cell fates and how cells accumulate errors and damage.[3] At the deepest level—that of the molecular interactions that govern gene expression—it is clear that substantial intracellular 'noise' is seen in protein production, which appears to be dominated by stochastic effects within the machinery for producing and destroying the messenger RNAs. Furthermore, some of this noise seems actually beneficial in helping to enhance the ways that molecular systems can detect and respond to internal signals.[5] The intrinsic hypermutability that acts within the immune system to generate capacity to recognize novel antigens is another instance of noise

that has adaptive value. For the most part, however, noise is disruptive.

Genome instability, which results in somatic mutations and chromosomal abnormalities, is an important source of intrinsic variation that interferes with normal function. In ageing mice, somatic mutation frequencies as high as 10^{-4} per gene per cell have been reported.[6] Epimutations may occur through loss or disruption of DNA methylation patterns, affecting gene expression. Genome instability also gives rise to mitochondrial DNA point mutations and deletions, which arise at a 10-fold greater rate than nuclear mutations and accumulate in certain tissues throughout life, causing impaired capacity to generate cellular energy. Intrinsic variability may arise during development affecting cell division and migration. The cumulative effects of intrinsic variations at the cell level during development are seen in the variability of organ size and cell number when morphogenesis is complete. In genetically identical individuals, such as inbred mice or monozygotic human twins, the variation in organ size can be large.[2] For example, the size of the ovary in individual newborn mice of the same strain may vary 3-fold,[7,8] and there can be differences of 10–20% in the sizes of the hippocampi in human twin pairs.[9] All these sources of variation are likely to have effects on the development, growth and ageing of individual organisms.

The agenda that flows from Gärtner's paper and related work is challenging. The role of intrinsic chance affecting important aspects of biology has been relatively neglected by mainstream biomedical research. Chance is, of course, recognized for its contributions to generating variability in data, where it is regarded as a nuisance rather than otherwise. However, the ideas that (i) chance represents a genuine third component beside environment and genotype and that (ii) the noise might actually constitute an important 'signal' about underlying biological mechanisms need to be better recognized.

In the specific context of ageing, there is particular reason to believe actions of chance to be significant. During development, many things can and do go wrong, but the strong action of natural selection on the early stages of life means that many developmental processes are 'canalized'. This strict control does not appear to extend to organ size variations that are likely to be inconsequential in youth but may become important in later life, when the power of natural selection is much reduced. Thus, the variations noted above in the sizes of ovary or hippocampus are unlikely to have detectable effects during the early and middle years of life but can at later ages affect reproductive decline or cognitive impairment, respectively. In terms of variations that contribute to pathophysiology of ageing, gerontologists already recognize that the force of natural selection declines progressively with age, which is why ageing is thought to be driven fundamentally by the gradual accumulation of cellular and molecular defects.[10] Thus, the idea that intrinsic variation is at play, resulting in significant non-genetic and non-environmental variation is seen increasingly to be important for our understanding of, and capacity to intervene in, the processes that lead to age-related frailty, disability and disease.

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