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Short Communication

How Human Longevity and Species Survival Could Be Compatible with High Mutation Rates

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Editor's Note: Anyone who has ever looked at the ease with which DNA is damaged finds the figures frightening. Most of your cells have incurred some DNA damage since you picked up this journal and some of that damage will go unrepaired. When this damage occurs to the germ-cell line, the results are likely to be fatal. Given the length of the human lifespan, it verges on the miraculous that there is a human species. The Gavrilovs offer an explanation of how we manage to survive.

DELETERIOUS MUTATIONS can substantially shorten the human life span. Given that harmful mutations are so numerous in human species (see below), it is not clear how the human species can survive, let alone be long-lived. Recently Eye-Walker and Keightley[1] found that humans suffer a surprisingly high genomic deleterious mutation rate—more than 1.6 new harmful mutations per person, per generation—which is close to the upper tolerable limit. In order to explain why we are not already extinct, Crow[2] suggests that deleterious mutations are eliminated through "genetic deaths"[3] in bunches rather than independently. Here, we discuss the problem further and explain the paradox of how the expected massive genetic deaths could be consistent with the observed low levels of human infertility and our remarkable longevity.

First, consider the recent controversy regarding whether the human infertility rate is high enough to be the main mechanism for the elimination of deleterious mutations. It is tempting to link the high mutation rate with Cummins' suggestion[4] "that humans have a strong hereditary predisposition to infertility." He based this conclusion mainly on recent claims that 30–50% of women were childless in the past, when no birth control was practiced.[5] These claims, however, came from the analysis of extremely incomplete historical data (dating back to as early as the year 740) when the births (and early deaths) of many children (especially daughters) were underreported. A more careful and reliable study has found that only 10% of married women were childless in the past, while, for women married at young ages (20–25 years), the proportion of childless women was even less—only 3%.[6] Thus, biologic infertility is a rare event in humans, and we should, therefore, focus on other possible mechanisms for the selective elimination of deleterious mutations.

We believe that the ideal mechanism for the selective elimination of mutations should operate early in life—through the selection of zygotes[7] rather than through infertility of adults. Genetic recombination (chromosomal crossing

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over) and random distribution of homologous chromosomes in meiosis create unique opportunities for reshuffling genetic assets and liabilities—a way to have some intact germ cells free of deleterious mutations among many germ cells with bunches of mutations. In this case, high mutation rates will not have a devastating effect on human populations (extinction via infertility) but will simply increase the mean number of attempts for parents to conceive a child.

This hypothesis of mutation mosaicism of germ cells predicts that a fertile couple would usually have its first child much later than 9 months after first coitus, because several attempts (that is, several monthly ovarian cycles) would be necessary to conceive successfully. Indeed, the mean interval from marriage (as an estimate of first coitus) to first birth (for fertile couples without contraception) is approximately 16–19 months depending on parental age.[6] This means that, on average, only 1 of 7–10 attempts to conceive is successful. Thus, high mutation rates may affect as many as 86–90% of zygotes with bunches of mutations, but the remaining 10–14% of unaffected zygotes will ensure human survival and likewise ensure that there is only a small proportion of childless couples, if most couples continue to engage in regular coitus.

The elimination of deleterious mutations via the selection of zygotes is more effective than elimination via adult infertility. Moreover, infertile adults are very dangerous to species survival—a conclusion that is recognized as the basis for the biologic control of insect populations via the artificial introduction of sterile species in the wild. This suggestion, the early elimination of deleterious mutations, is also consistent with the paradoxically low correlation that is seen between lifespan and factors that affect mutation rates.

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