Happy People Live Longer

Bruno S. Frey

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damental speciation, extinction, and morphological and behavioral milestones that ultimately produced those traits that define us as human and distinguish us from other primates (*4*, *5*, *21*). On the basis of an analysis of coexisting East African hominin and bovid fossil assemblages, Reed (*23*) concluded that "*Homo* species appear the first to be adapted to open, arid environments."

One strategy articulated in the NRC report (*4*) is to investigate the key evolutionary milestone events as natural history experiments. The grand challenge will be to develop coordinated sets of observations to test proposed links between African climate and faunal change. The foremost task will be to improve the fossil and paleoclimate records, especially for those intervals where available evidence is most suggestive of climatic forcing of adaptive evolutinary change.

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PSYCHOLOGY

Happy People Live Longer

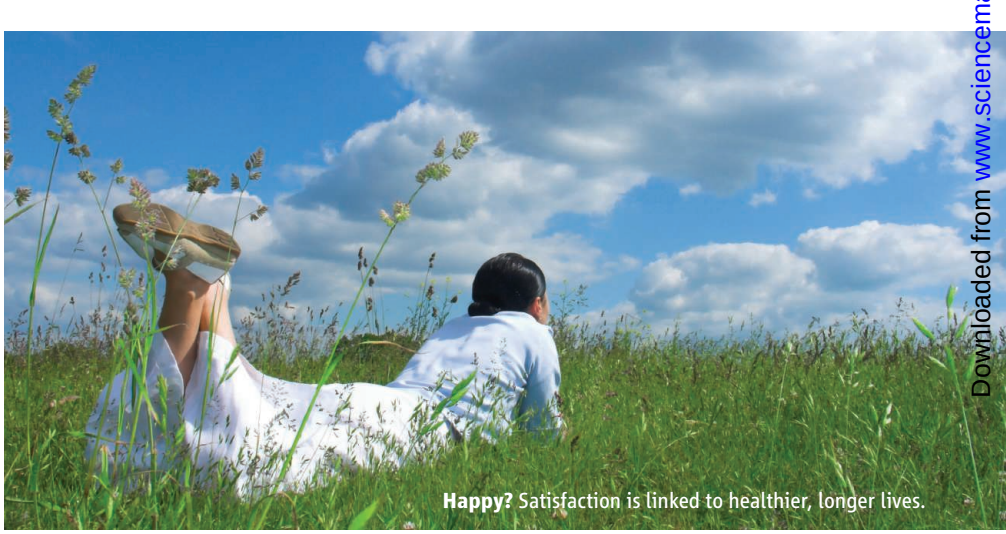
The pursuit of happiness can have concrete benefits for well-being.

Bruno S. Frey

There is a longstanding idea that happiness causes people to live longer, healthier lives. However, convincing evidence that subjective well-being (the more scholarly term for happiness) contributes to longevity and health has not been available. Recently, however, social psychologists Diener and Chan (*1*) showed that many kinds of studies, using different methods, conclude that happiness has a positive causal effect on longevity and physiological health.

Previous studies had offered widely different and competing findings. Some found no causation or reverse causation, in particular that healthy people are happier (which is undisputed) (*2*). Others suggested that unidentified, unobserved factors influence both happiness and longevity and health. Diener and Chan's survey presents solid evidence for the benefits of happiness. For example, a meta-analysis (*3*) based on 24 studies estimated that happy people live 14% longer than persons who report that they are unhappy. In a survey of people living in industrial countries, happier people enjoy an increased longevity of between 7.5 and 10 years (*4*). Happier people are also less likely to commit suicide, and they are less often the victims of accidents.

How can researchers measure the influence of happiness on physical health and longevity? One important method is the longitudinal study, in which investigators follow individuals over many years, to identify whether the happier ones live longer. The "nun study" (*5*) has become particularly famous. Nuns are well suited for a longevity study because they live under very similar conditions. Before young women entered a monastery, researchers asked them about their subjective happiness level. Those who perceived themselves to be happier died at a median age of 93.5 years. In contrast, those who considered themselves to be less happy died at a median age of 86.6 years.



Happy? Satisfaction is linked to healthier, longer lives.

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Researchers can also examine how external, or exogenous, factors that induce changes in happiness are related to specific physiological processes known to affect health and longevity. Emotions can be manipulated in laboratory experiments, for instance, by showing subjects a joyful or a sad film. Investigators can then measure how particular physiological factors, such as blood pressure, change. The effect on happiness of naturally occurring events, such as tempests, inundations, and earthquakes, also can be analyzed. Researchers also study how personal shocks, such as losing a companion, affect health. For example, one study (*6*) finds that the mortality of

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men who lose their wives doubles in the first month after the event. For women, the mortality rate after losing their husbands is three times higher than normal. So far, however, an effect of happiness on specific types of illness has not been established. In particular, Diener and Chan note that studies that have explored how happiness influences the outcomes of cases of metastatic cancer have produced findings that are unclear and unconvincing.

Philosophers such as Aristotle consider happiness to be the major goal most people aspire to in life (*7*, *8*). The findings discussed here make the pursuit of happiness even more important, since they demonstrate that high measures of life satisfaction and positive emotions strongly contribute to better health and a longer life. Future research needs to focus in more depth on the processes causing happy people to live longer and to be in better health. In addition, the costs of raising happiness by policy interventions should be compared to the costs of influencing longevity and health by other pathways.

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CELL BIOLOGY

A Translational Pause to Localize

Cells optimize the response to protein stress by controlling the localization and splicing of an mRNA that encodes a transcription factor.

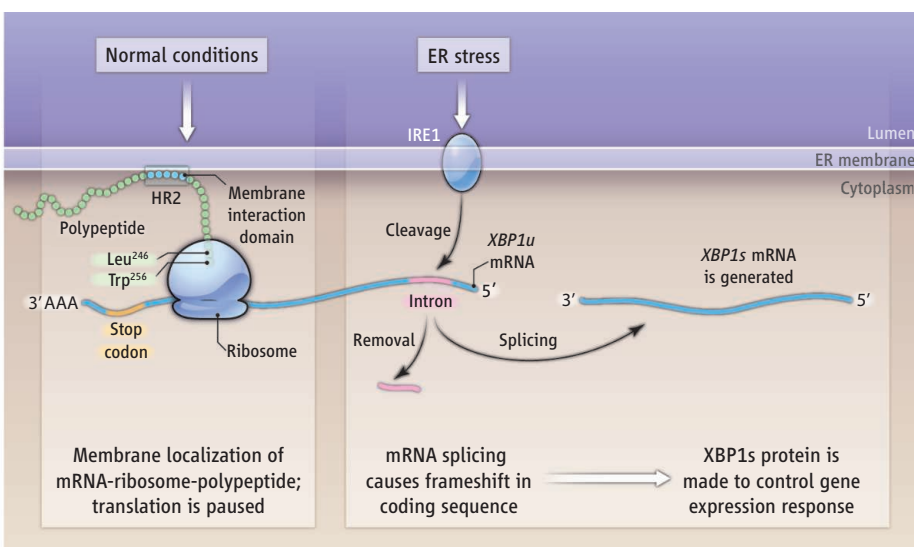
David Ron[1] and Koreaki Ito[2]

The unconventional splicing of a messenger RNA (mRNA) is key to a mechanism that controls the cellular response to unfolded proteins that accumulate in the endoplasmic reticulum (ER). Mammalian cells attempt to counterbalance this state of stress by expressing specific genes through the transcription factor XBP1 (*1*). The synthesis of this transcription factor requires splicing to generate its encoding mRNA, a process that occurs at the cytoplasmic face of the ER membrane. On page 586 of this issue (*2*), Yanagitani *et al*. reveal how translational pausing of the mRNA to be spliced contributes to this localization. The finding reveals surprising similarities in mechanisms regulating translation in eukaryotes and prokaryotes.

An imbalance between unfolded proteins and chaperones (which assist protein folding) in the ER activates IRE1, an enzyme that spans the ER membrane. IRE1 cleaves mRNA that encodes XBP1 at two sites, thereby excising a small intron. Cleavage is followed by ligation of the remaining mRNA fragments (*3*, *4*). This unconventional splicing is an important switch in the cell's unfolded protein response (UPR) because it shifts the reading frame of the mRNA to be translated (*5*, *6*). The products of unspliced *XBP1* mRNA (*XBP1u*) and spliced mRNA (*XBP1s*) share a common amino terminus, but diverge at their carboxyl termini; whereas XBP1s is a potent activator of UPR target genes, XBP1u is an unstable repressor (*7*).

In mammalian cells, unspliced *XBP1u* mRNA is constitutively associated with the ER membrane under normal conditions (*8*). This localization—unusual for an mRNA encoding a soluble protein—is mediated by a hydrophobic region (HR2) at the carboxyl terminus of the XBP1u protein. HR2 of the nascent polypeptide chain is thought to interact directly with the ER membrane and thus recruits the associated mRNA–ribosome-nascent chain complex to the cytoplasmic face of the ER membrane. *XBP1u* mRNA lacking the region encoding HR2 is cytosolic, as is the spliced *XBP1s* mRNA, which, due to the frame shift, no longer encodes HR2 (*9*).

However, this proposed mechanism for tethering the *XBP1u* mRNA to the ER by its associated nascent chain presents a problem: the sequence encoding HR2 is at the 3′ end of *XBP1u* mRNA and is separated from the stop codon by a mere 53 amino acids (in humans). At average rates of translation by the ribosome (one to two peptide bonds per second), HR2 would be exposed on ribosome–nascent chain complex for only a brief period, before termination of translation would release the polypeptide, severing the link between the mRNA and the ER-bound XBP1u protein. Given its position on the XBP1u polypeptide chain, how can HR2 contribute to localization of the ribosome–nascent chain complex?



Temporary time-out. To be poised for rapid splicing in response to the accumulation of unfolded proteins in the ER, unspliced *XBP1u* mRNA is tethered to the ER membrane by the paused ribosome–nascent chain complex. Pausing requires interactions of Leu^{246} and Trp^{256} in the nascent chain with the ribosome. The pause stabilizes the complex, favoring cleavage of *XBP1u* by IRE1. This causes a frame shift in the coding sequence of the spliced *XBP1s* mRNA, which precludes translation of Leu^{246} and Trp^{256} and relieves the pause. The newly translated transcription factor XBP1s activates genes that counter unfolded protein stress in the ER.

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