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Commentary

Free Radical Theory of Aging at 70: Adaptive Homeostasis and the Modern Revision of a Classic Hypothesis

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Denham Harman's free radical theory of aging, first articulated in the mid-1950s, proposed an elegantly simple mechanism for senescence: metabolism generates reactive byproducts, those byproducts accumulate as molecular damage, and accumulated damage is aging. Seven decades on, the theory remains one of the most cited frameworks in biogerontology, but its core causal claim has been substantially reworked rather than confirmed. According to PubMed, the free radical theory of aging has provided a theoretical framework for an enormous amount of work and significant advances in understanding aging, and up to the turn of the century it received abundant support from fields ranging from comparative physiology to molecular biology, with work showing that overexpression of antioxidant enzymes increases lifespan. The trouble is that subsequent work did not simply extend the theory; it began to contradict its central prediction.

The pivotal complication is that Reactive Oxygen Species (ROS) turned out to be more than incidental damage. A landmark review of this shift noted that other laboratories have shown that in some cases there is simultaneously increased oxidative stress and increased longevity, and the discovery that free radicals can serve as signals rather than purely as damaging agents led to the proposal that they act as modulators of physiological processes-for instance, ROS stimulate physiological adaptations to physical exercise. This reframing did not emerge from a single study but from a convergence of evidence across model organisms, encapsulated in the concept of mitochondrial hormesis, or mitohormesis.

The mitohormesis concept holds that a transient increase in mitochondrial ROS production-rather than constituting unmitigated damage-can act as a retrograde signal that triggers a compensatory adaptive response, ultimately reducing long-term oxidative stress and extending lifespan. According to PubMed, the foundational articulation of this idea explained that in conflict with Harman's free radical theory of aging, the lifespan-extending effects of calorie restriction and reduced glucose metabolism in organisms ranging from yeast to mice may be due to increased mitochondrial ROS formation causing an adaptive response that culminates in increased stress resistance and a long-term reduction of oxidative stress, a phenomenon named mitochondrial hormesis. Crucially, this framework was explicitly extended to exercise physiology: this mitohormetic response may also apply to the health-promoting effects of physical exercise in humans, and consistently, blocking the mitochondrial ROS signal with antioxidants impairs the lifespan-extending and health-promoting capabilities of both glucose restriction and physical exercise.

A follow-up synthesis extended this evidence base across additional model systems and made the challenge to classical theory explicit. According to PubMed, this review found that several longevity-promoting interventions across yeast, nematodes, fruit flies, mice, rats, and possibly primates and humans appear to converge by activating mitochondrial oxygen consumption and increasing ROS formation, which act as molecular signals inducing endogenous defense mechanisms that culminate in increased stress resistance and longevity-an adaptive response termed mitohormesis. The authors were direct about the theoretical stakes, concluding that antioxidant supplements that prevent these ROS signals interfere with the health-promoting and lifespan-extending effects of calorie restriction and exercise, and that, taken together, these findings question Harman's free radical theory of aging, suggesting instead that ROS act as essential signaling molecules promoting metabolic health and longevity.

Genetic evidence in Caenorhabditis elegans has reinforced this picture at the mechanistic level. According to PubMed, mutants with partial loss-of-function in mitochondrial electron transport chain subunits exhibit increased longevity, and researchers found that the generation of mitochondrial superoxide is elevated in these long-lived mutants, and this elevation is both necessary and sufficient to increase longevity, since it is abolished by antioxidants and phenocopied by mild treatment with a pro-oxidant. The authors explicitly stated that these findings are not consistent with the mitochondrial oxidative stress theory of aging, and instead show that increased superoxide generation acts as a protective signal that triggers gene-expression changes attenuating the effects of subsequent aging.

Perhaps the most consequential blow to the classical theory, however, came not from model organisms but from human

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epidemiology. According to PubMed, a major reassessment observed that a critical blow to the free radical theory of aging came from epidemiological studies showing that antioxidant supplementation did not lower the incidence of many age-associated diseases and, in some cases, increased the risk of death. Combined with the molecular evidence that elevated ROS can promote rather than shorten lifespan, the authors framed the field as standing at a genuine crossroads, noting that gerontologists interested in free radical biology require new insights to clarify the true role of ROS in aging, and proposed reframing the original hypothesis as a "cell signaling disruption theory" rather than a simple damage-accumulation model.

None of this erases Harman's original insight that oxidative damage accumulates with age and contributes to senescence; mitochondrial-targeted antioxidant interventions in animal models continue to demonstrate measurable effects on healthspan in specific disease contexts. What has changed is the framework's exclusivity. Seventy years after its formulation, the free radical theory of aging survives not as a single linear damage hypothesis but as one component nested within a broader, more dynamic model of redox signaling and adaptive homeostasis-one in which the dose, timing, and context of oxidative stress matter as much as its mere presence.

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