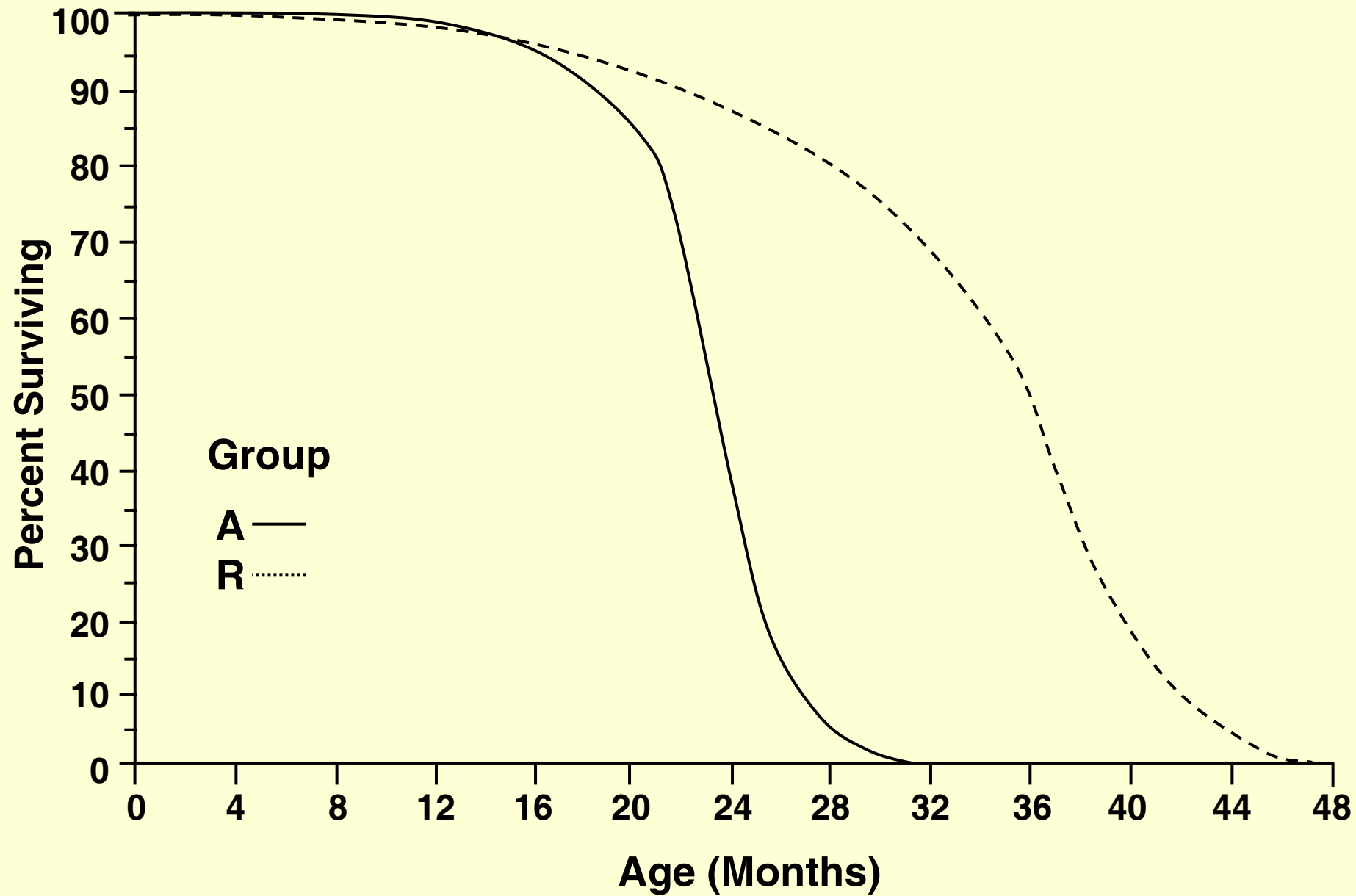


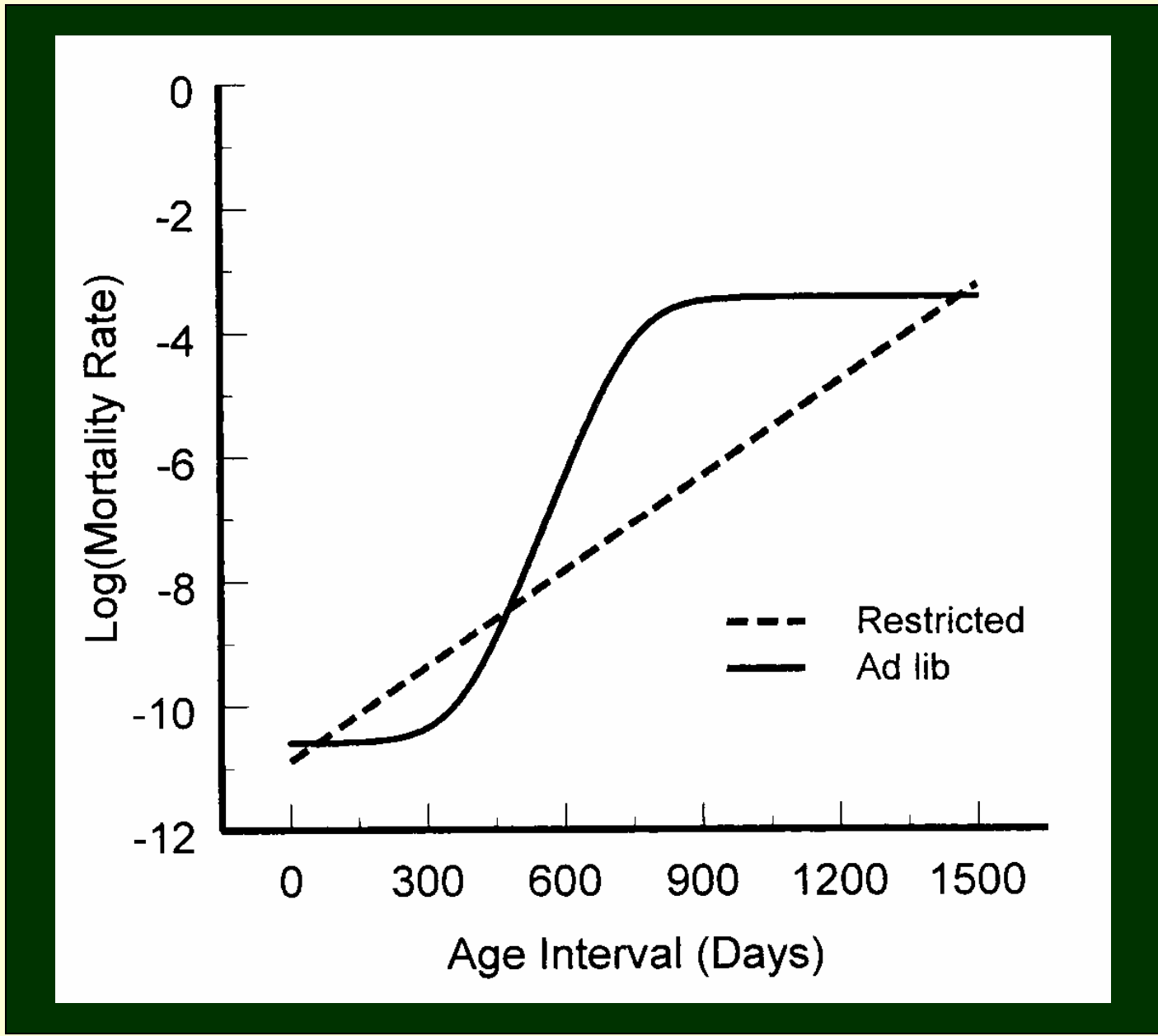
The Role of Hormesis in Life Extension by Caloric Restriction

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Pletcher et al., J. Geron: BS, 55A:386, 2000

Dietary Restriction Delays the Occurrence or Slows the Progression of Age-Associated Diseases

Examples from studies with male F344 rats:

Chronic nephropathy:

Progression slowed; at death 68% of AL and 1% of DR with severe lesions.

Cardiomyopathy:

Progression slowed; at death 19% of AL and 6% of DR with severe lesions.

Leukemia/Lymphoma:

Occurrence delayed; at death prevalence of 23% in AL and 30% in DR.

Many Physiological Characteristics Are in a More Youthful State at Advanced Ages in Animals on a Long-Term CR Regimen

This occurs by 2 different routes:

- 1. CR doesn't affect the characteristic on its initiation in the young animal, but slows the age-associated change in the characteristic; example: CR does not affect serum cholesterol level when initiated in young rats but slows the age-associated increase in its level.**
- 2. CR influences the characteristics at or near the time of initiation in the young animal, but does not slow the age-associated change in the characteristic; example: CR increases the rate of hepatic protein synthesis in the young rat , but does not slow the age -associated decrease in protein synthesis.**

A Recent Challenge to the Concept that Food Restriction Extends Life by Reducing Caloric Intake

In both rats and mice, a marked reduction in the intake of methionine has been found to extend life to about the same extent as a 40% reduction in food intake. Moreover, it is claimed that food intake was not decreased in the rodents on the reduced methionine intake.

This finding has led to some to suggest that term caloric restriction (CR) should be replaced by dietary restriction (DR).

Life Extension of Male F344 Rats by Food Restriction (FR)[#]

DIETARY GROUP	N	MEDIAN SURVIVAL (DAYS)	10 TH PERCENTILE SURVIVAL (DAYS)
Ad Lib-Fed	60	730 (708-764)*	857 (819-961)*
40% FR	60	936 (883-984)*	1121 (1080-1168)*
40% FR without protein or methionine restriction	60	956 (906-1028)*	1158 (1125-1230)*

[#]Data from Masoro et al.

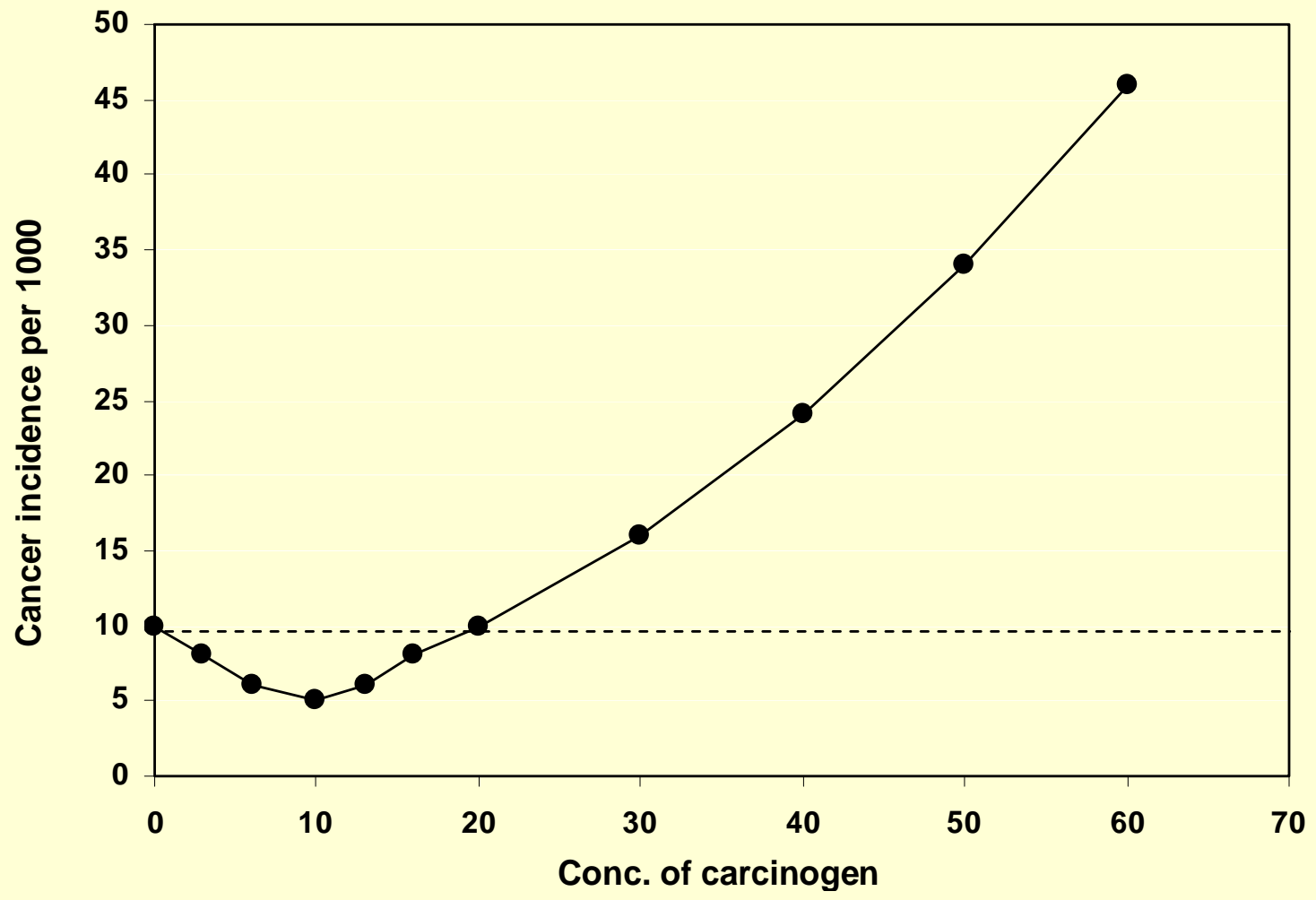
*Numbers in parentheses are 95% confidence intervals; both restricted groups differed significantly from the ad libitum-fed group ($P < 0.001$) but not from each other at the $P < 0.05$ level.

Hypotheses on Anti-Aging Action Mechanisms of DR

- 1. Retardation of Growth & Development Hypothesis**
- 2. Reduction of Body Fat Hypothesis**
- 3. Enhanced Apoptosis Hypothesis**
- 4. Decreased Body Temperature Hypothesis**
- 5. Increased Physical Activity Hypothesis**
- 6. Oxidative Damage Attenuation Hypothesis**
- 7. Modulation of Glycemia & Insulinemia Hypothesis**
- 8. Hormesis Hypothesis**

Concept of Hormesis

Classic Definition: Hormesis refers to the phenomenon in which the response to a chemical or physical agent is qualitatively different when the agent is of high intensity than when it is of low intensity.



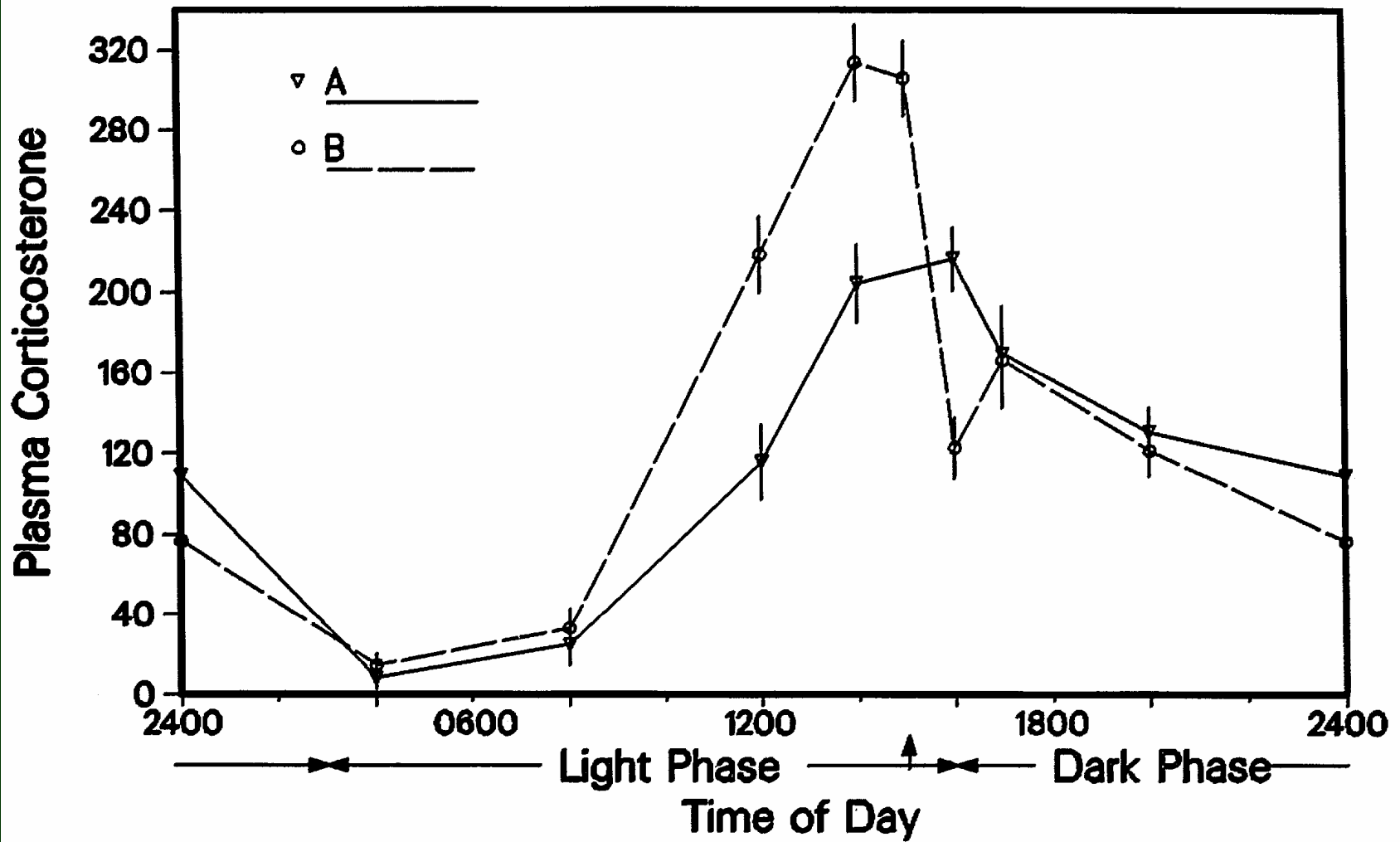
Rattan's Concept of Hormesis in Regard to Aging

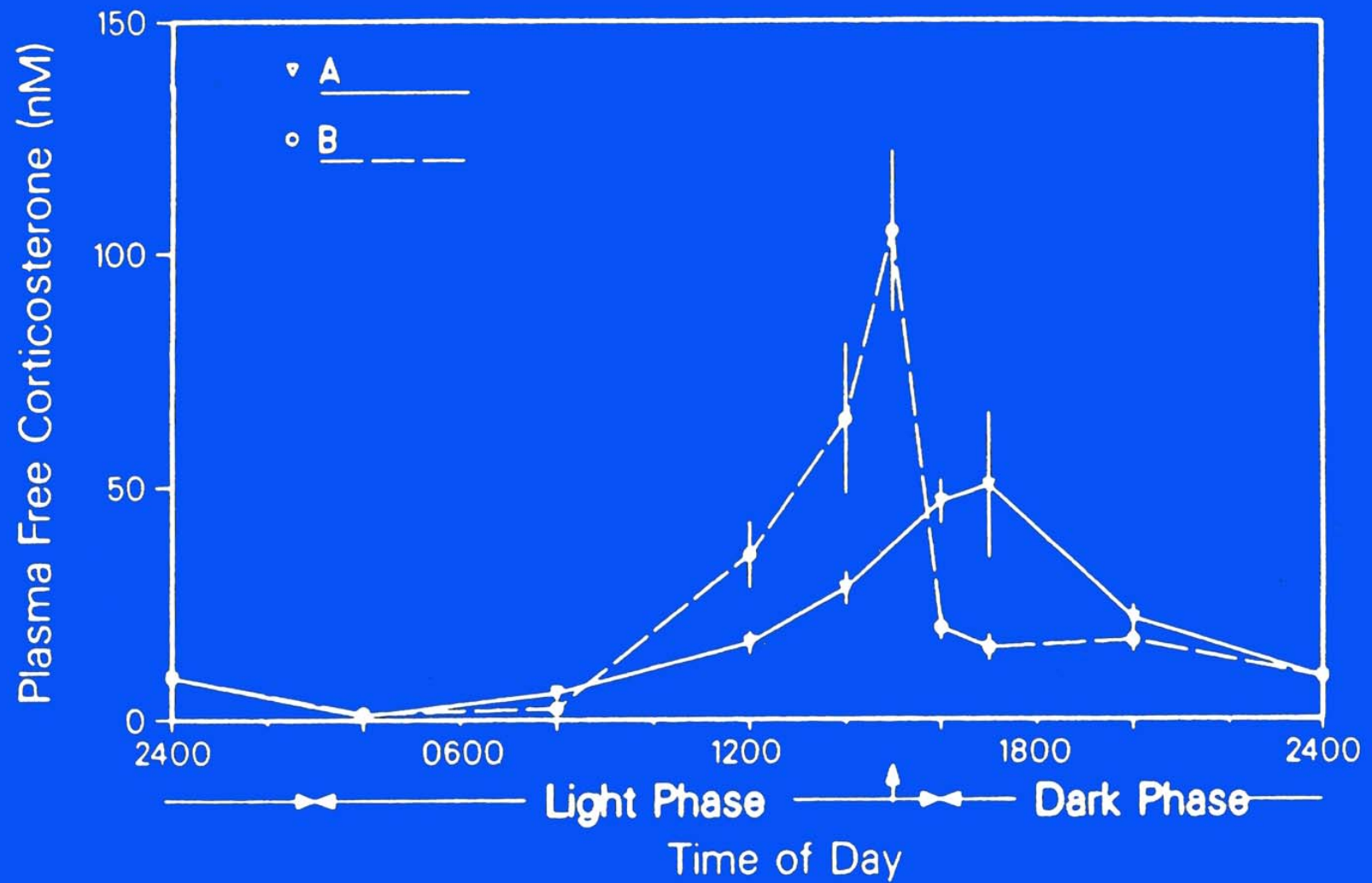
Rattan's Definition: Hormesis refers to beneficial effects resulting from the cellular responses to mild, repeated stress.

Rattan further proposed that hormesis as an aging retardant is based on the principle that repeated exposure to mild stress stimulates maintenance and repair processes.

**Is CR a Repeated
Long-Term Stressor?**

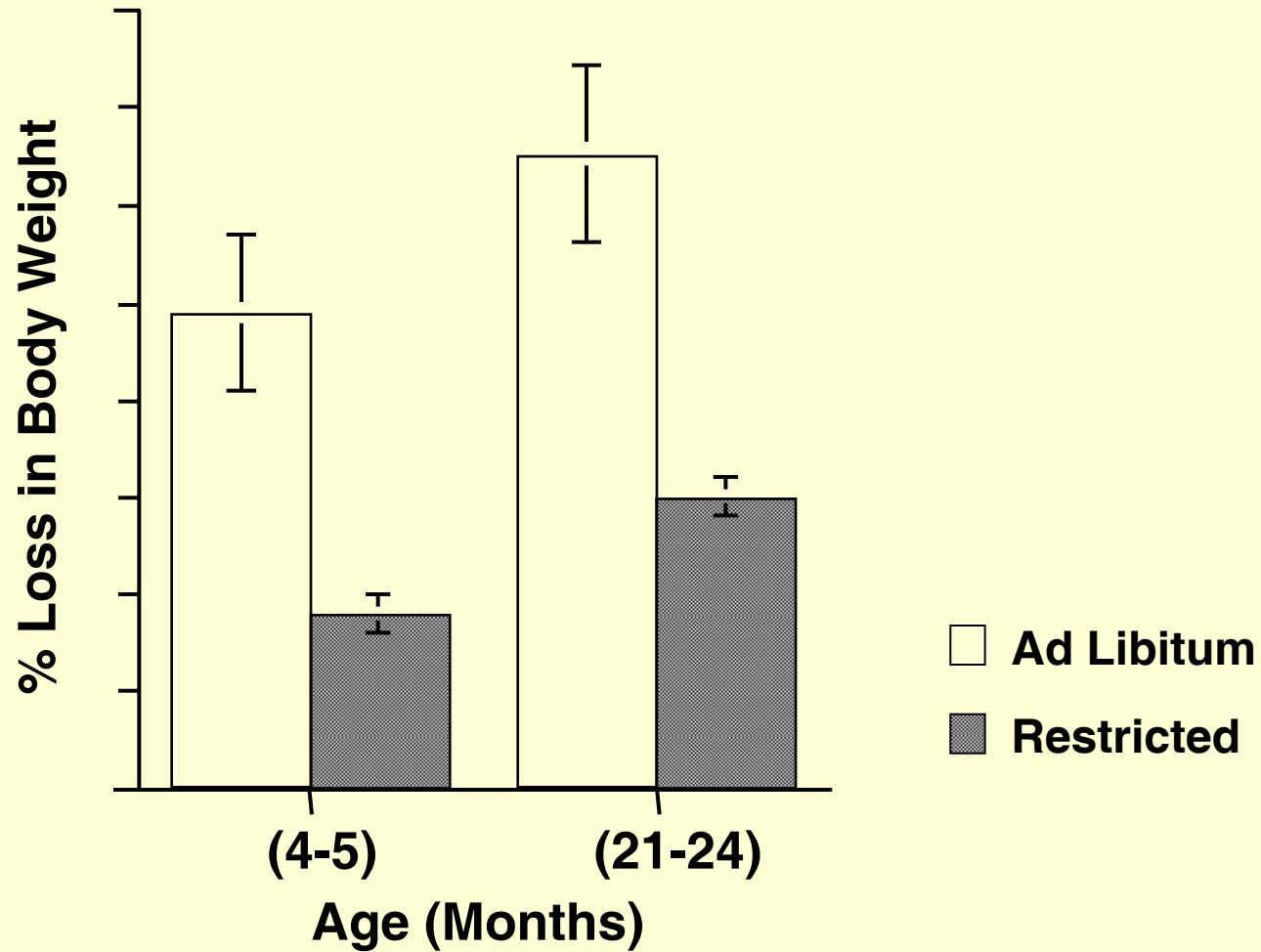
Corticosterone - 3-7 Months



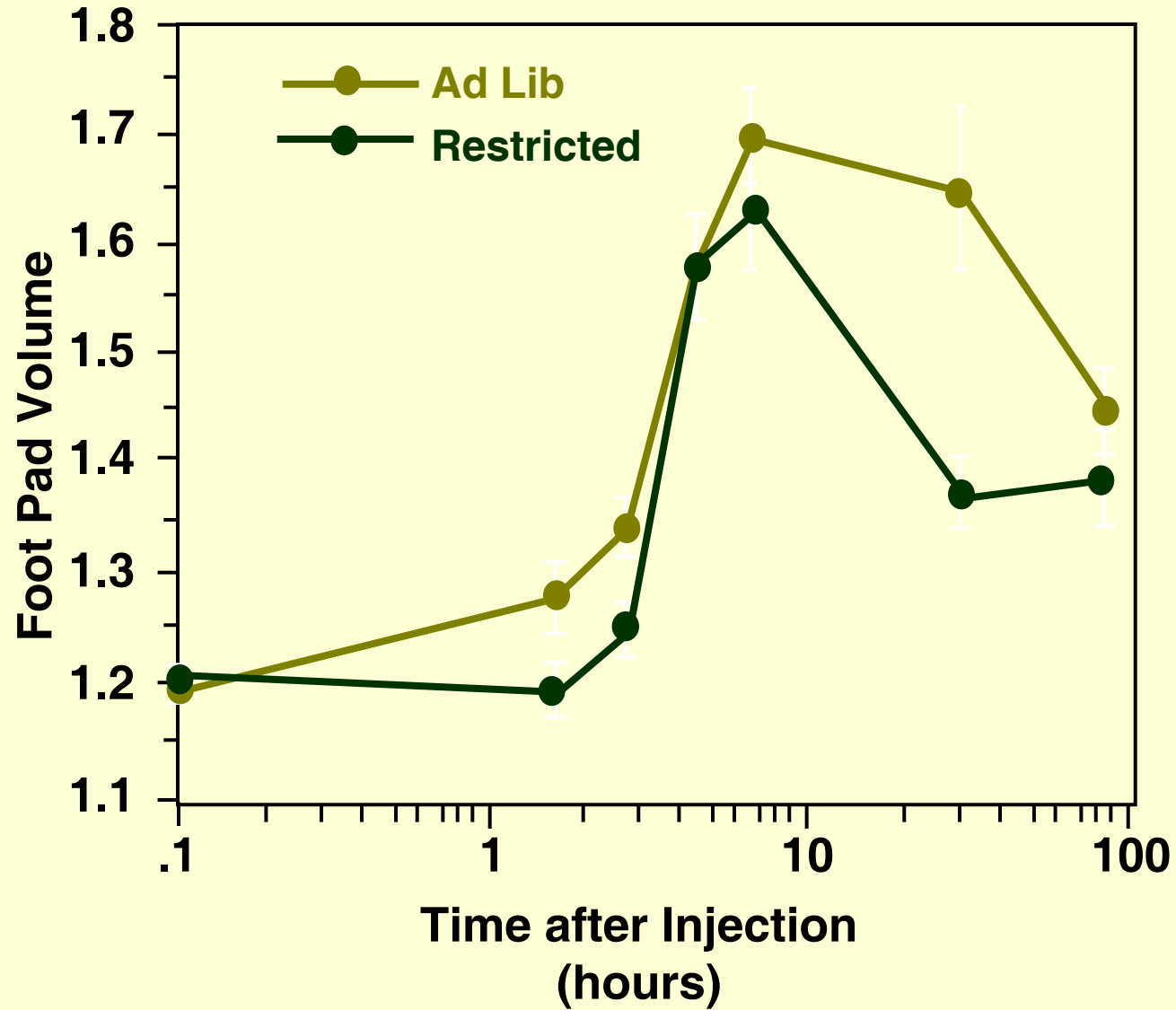


Does DR protect rats and mice from the damaging action of harmful agents?

Percent Loss of Body Weight during 48 Hr Following Surgical Implantation of Jugular Canula



Effect of Food Restriction on Carrageenan-Induced Edema



Klebanov, Stavinoha, Diais, Suh & Nelson (unpublished)

Ability of 20-Month-Old Male F344 Rats to Survive Heat Stress

Number of Rats Percent Survival

Ad Libitum-Fed	92	16
Dietary Restriction	36	75

Duffy et al. (1995) report that Dietary Restriction protects rats from the damaging action of toxic chemicals.

CR Meets Classic Criterion of Hormesis

A marked reduction of food intake is clearly harmful to the point of being lethal, while long-term moderate reduction of food intake enables the organism to more successfully cope with damaging environments and toxic agents.

How Does CR Hormesis Action Relate to Its Anti-Aging and Life-Extending Effects?

Kirkwood's Disposable Soma Theory poses that aging occurs because the energy used for protective and repair processes is less than that required for indefinite survival. Moreover, the rate of aging increases as the magnitude of the imbalance increases. Thus, by enhancing protective and repair processes, hormesis should act to slow the rate of aging.

Other Low-Intensity Stressors Extending Life

Low-Intensity Stressor

Species of Organism

Heat

Drosophila melangogaster;
Caenorhabditis elegans;
Saccharmyces cervisiae

Hypergravity

Drosophila melangogaster

Osmotic

Saccharmyces cervisiae

Evidence from Genetic Studies

Long-lived Mutants

Yeast

C. elegans

D. melanogaster

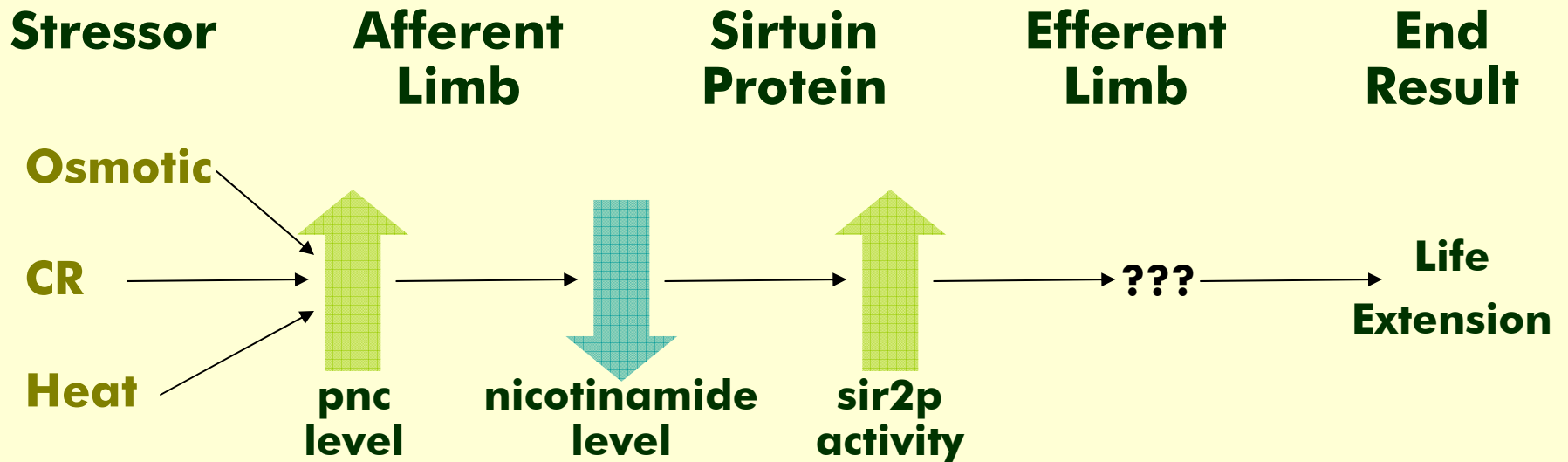
Increased Resistance to:

Heat stress, starvation, ethanol

Heat stress, reactive oxygen species, UV light

Starvation, desiccation, ethanol, paraquat

Pathway Proposed for *S. cerevisiae* by Sinclair Group



Another Possible Mechanism Underlying This Protection:

**DR increases and maintains the
ability to induce heat shock
proteins (hsp70).**

Effects of Age and DR on Induction of hsp 70 Expression on Hepatocytes from Male F344 Rats

Age (mos)	Induction of hsp 70	
	Ad Libitum Fed	Dietary Restricted
4-6	2.15 ± .38	3.05 ± 0.27
26-28	1.17 ± 0.33	2.38 ± 0.32

Enhancement of Repair Processes May Also Be a Component of Hormetic Pathway

- **CR enhances the repair of transcribed strands of DNA in rats.**
- **CR enhances the rate of whole-body protein turnover in rats.**

Work of Pashko and Schwartz on Carcinogenesis

CR's ability to protect mice against chemically induced tumors is lost if the animals have been adrenalectomized. Schwartz and Pashko proposed that elevated levels of adrenal steroids underlie the ability of CR to inhibit both carcinogen-induced tumors and those that occur spontaneously with advancing age.

Findings not in Accord with Hormesis Hypothesis

- **Neafsey's Criticism**
- **Sapolsky's work on elevated levels of glucocorticoids and aging**
- **CR does not increase resistance to all intense stressors**

CR Does Not Increase Resistance to All Intense Stressors

Skin wound healing

Coping with low environmental temperatures

Some immune system responses

Reasons Most Biogerontologists View Hormesis Unimportant in the Life-Extending Action of CR

- **Most biologist have long discounted the biological importance of hormesis**
- **McEwen's concept of allostatic load**

Hormesis Provides a Unifying Framework That Embraces Several of the Other Proposed Hypotheses Regarding the Life-Extending and Anti-Aging Actions of CR.

Hormesis Not Likely the Only General Processes Underlying the Life-Extending and Anti-Aging Actions of CR.

**The other likely process is a decreased
rate of generation of damaging agents.**

An Imperative Is to Test the Hormesis Hypothesis by Studies with Potential of Falsifying It

It is difficult to design such studies for the following reasons:

- **Hormesis is likely only one of two general processes underlying the actions of CR.**
- **It is likely that two or more pathways underlie the hormetic process.**

Summary of the Hormesis Hypothesis

- 1. Enabled animals in the wild to survive unpredictable and relatively brief periods of food shortage.**
- 2. The anti-aging action resulting from sustained restriction of food (DR) is a byproduct of this evolution.**
- 3. Two likely proximate mechanisms of this hormesis have been identified but much remains to be learned in this regard.**