

Ethology:

Considering both the environment
and
the individual's biological responses
to study
cancer risk and progression across the lifespan

Martha McClintock. Ph.D.

A Transdisciplinary Approach

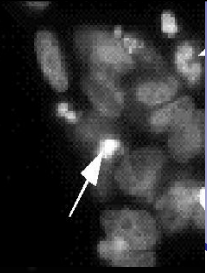
The cancer cell story ---- The social isolation story



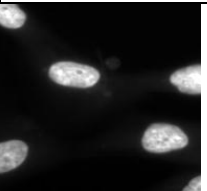
Conzen MD Lab

GCs inhibit chemotherapy-induced apoptosis in mammary epithelial **CELLS**

Paclitaxel



Paclitaxel+ GC



Does an altered stress response promote mammary tumor growth?

McClintock PhD Lab:

Social isolation and roles increase cort stress response and naturally-occurring mammary gland tumors in Sprague- Dawley **RATS**

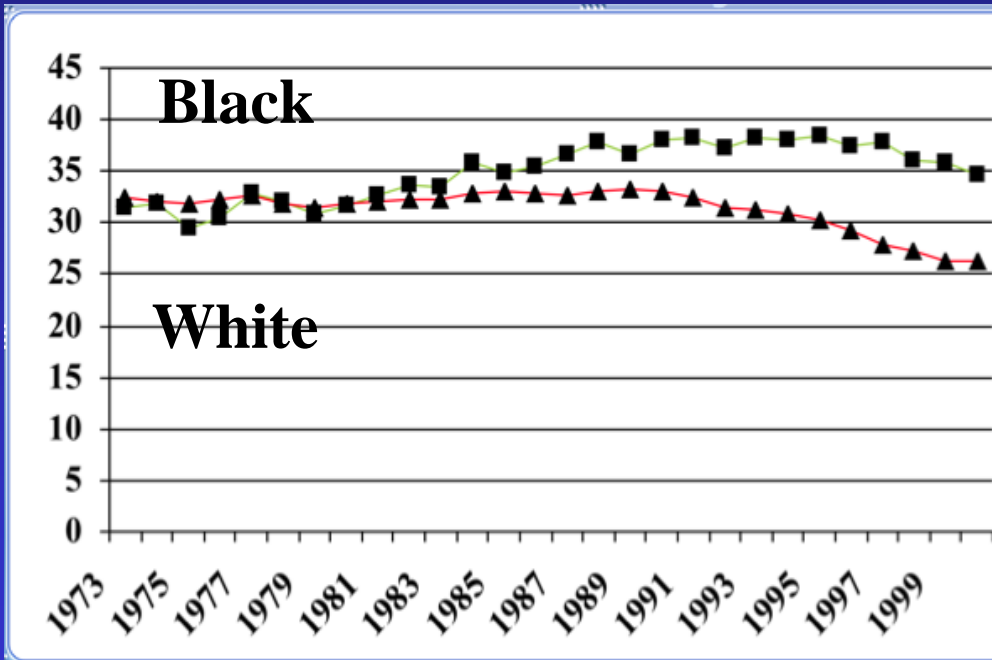
NATIONAL
CANCER
INSTITUTE



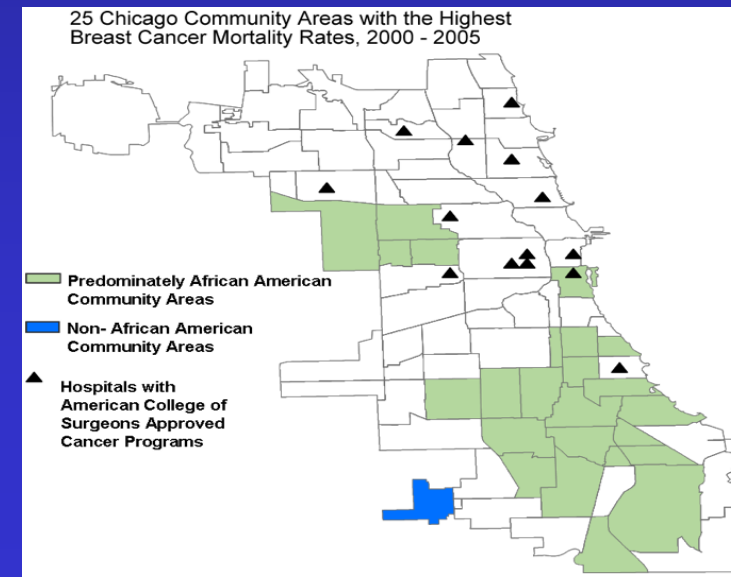
Gene Flow

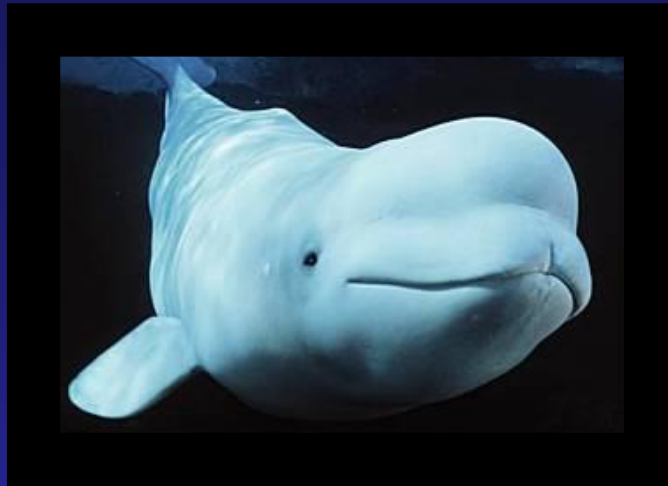
Health Disparities In Breast Cancer Mortality

WHY?



Racism and Inequity





**Natural
Mammary
Cancers**



Ethology:

Mechanisms AND Evolutionary Function

Mammary Glands Evolved To Function In A Range of Environments

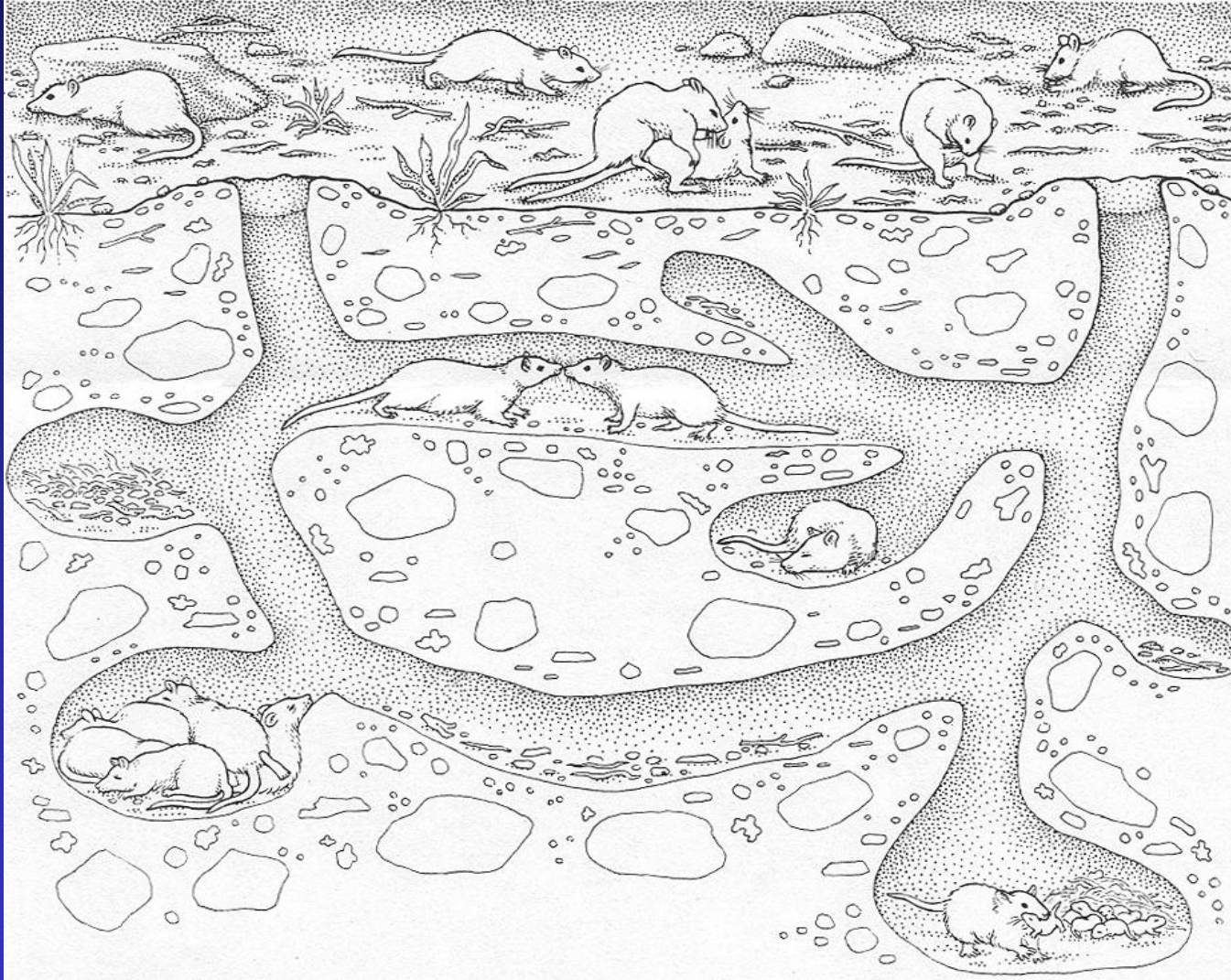


**Mammary Glands Evolved To Conserve
Energetics During Exposure to Stressors
To Protect Milk Production**



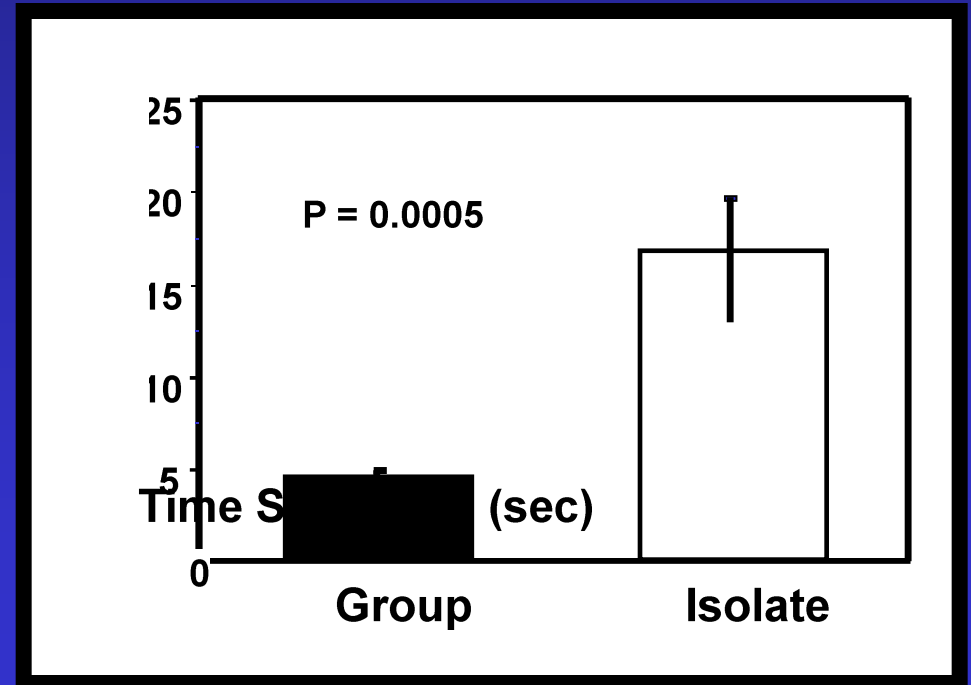
Dorothea Lange 1936

Mammals Evolved to Survive and Reproduce In Diverse Natural Environments



Facultative Responses: each individual has the capacity for different responses

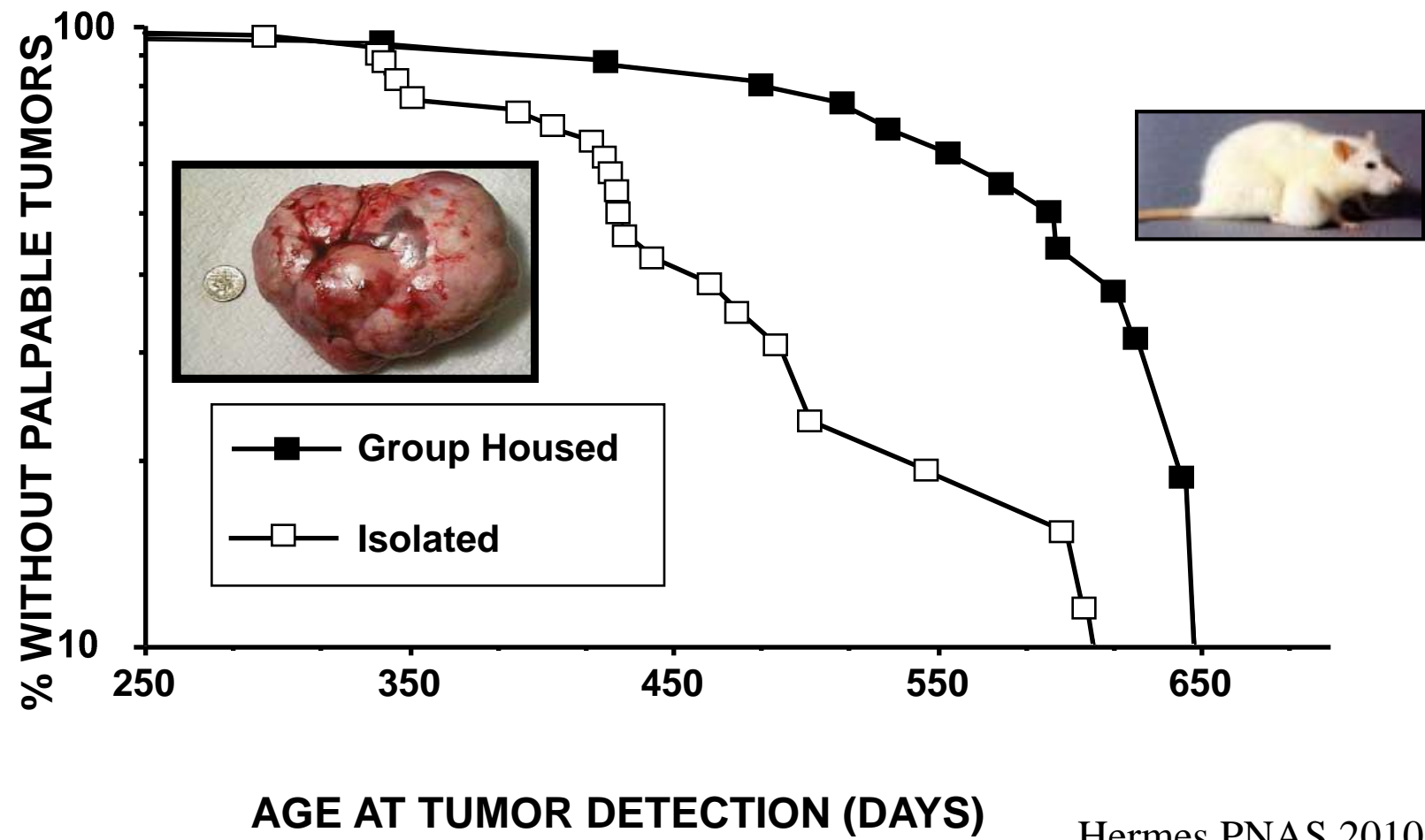
Sentinel Role And Vigilance Among Rats

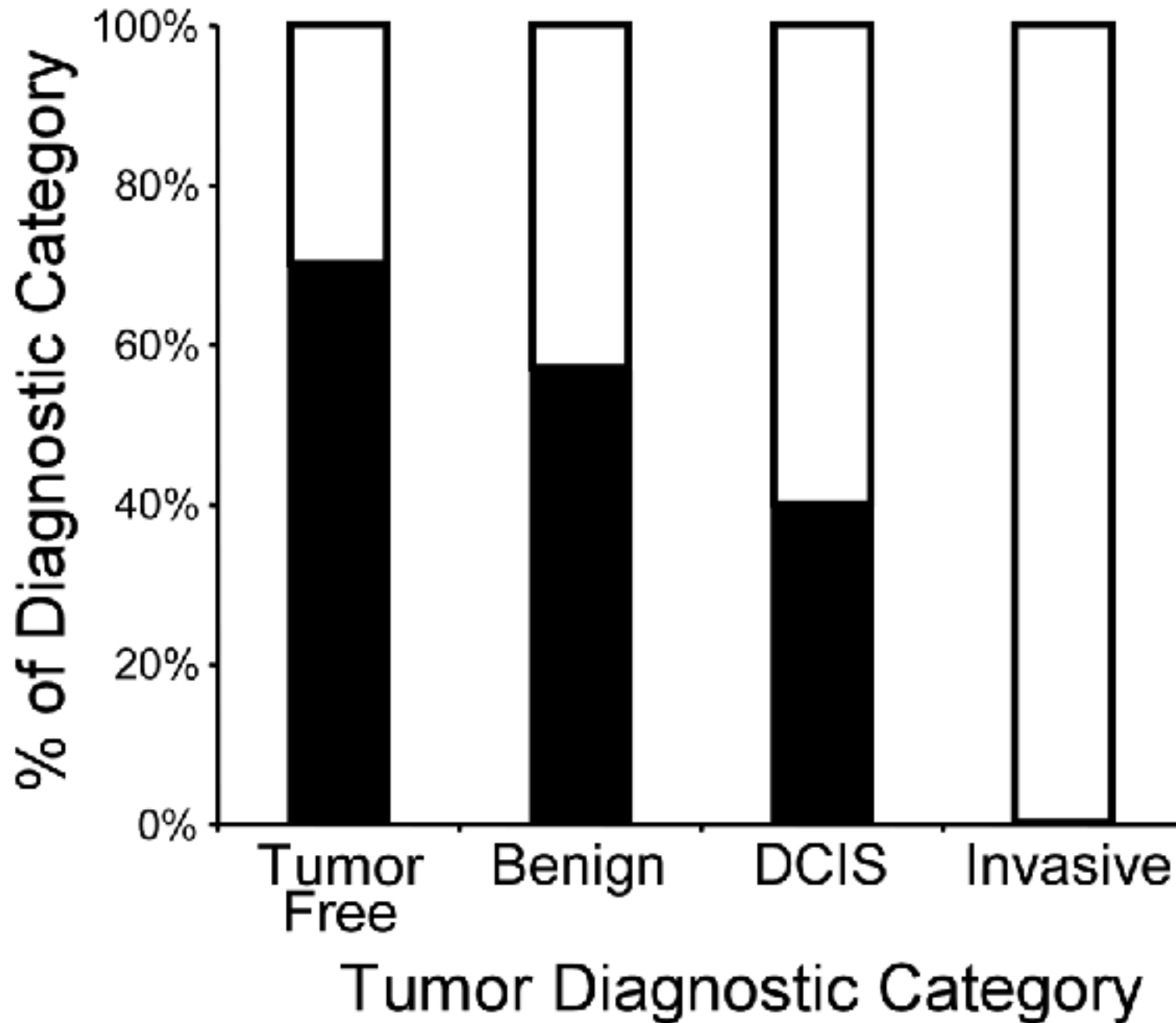


Social Dynamics During An Everyday Stressor



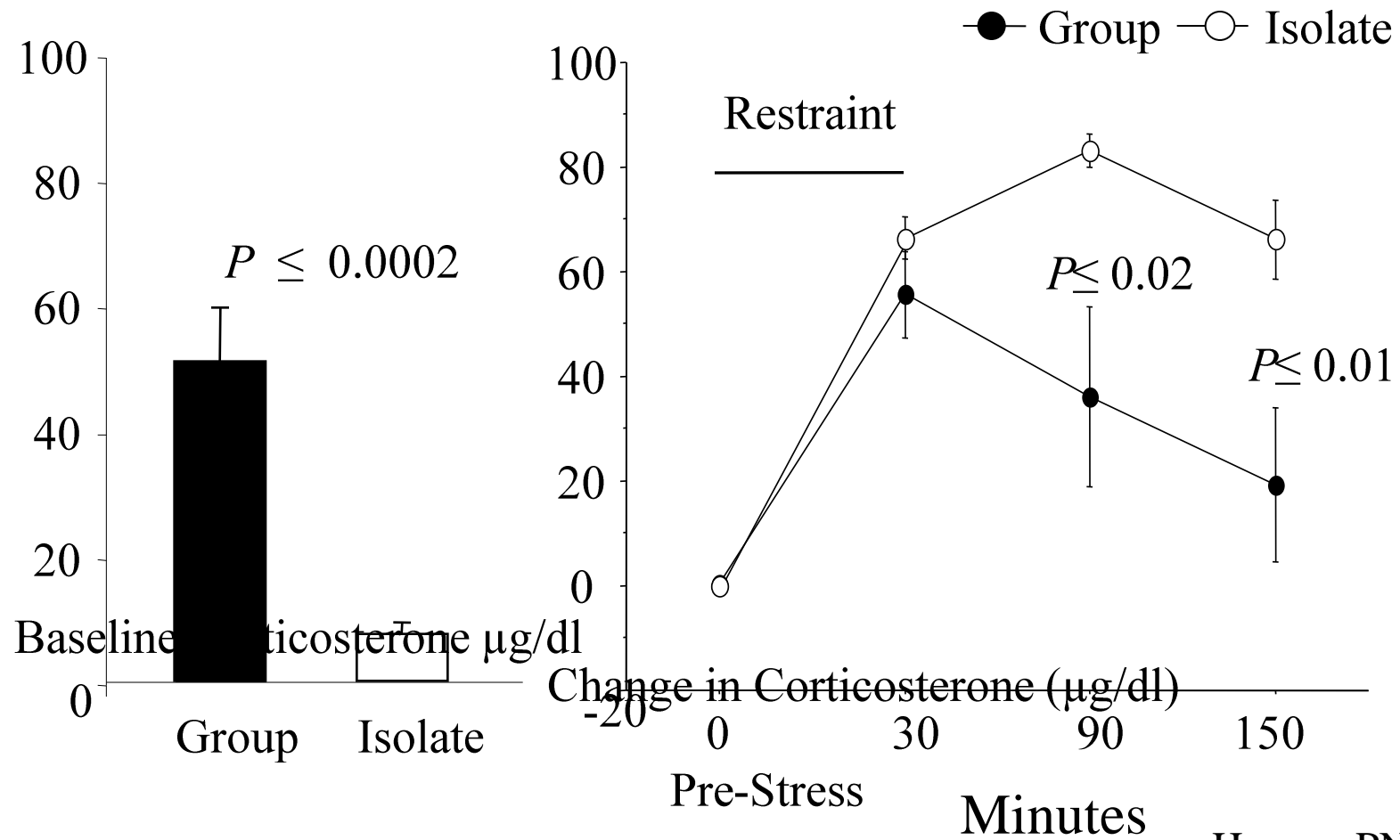
Spontaneous Mammary Tumor Development



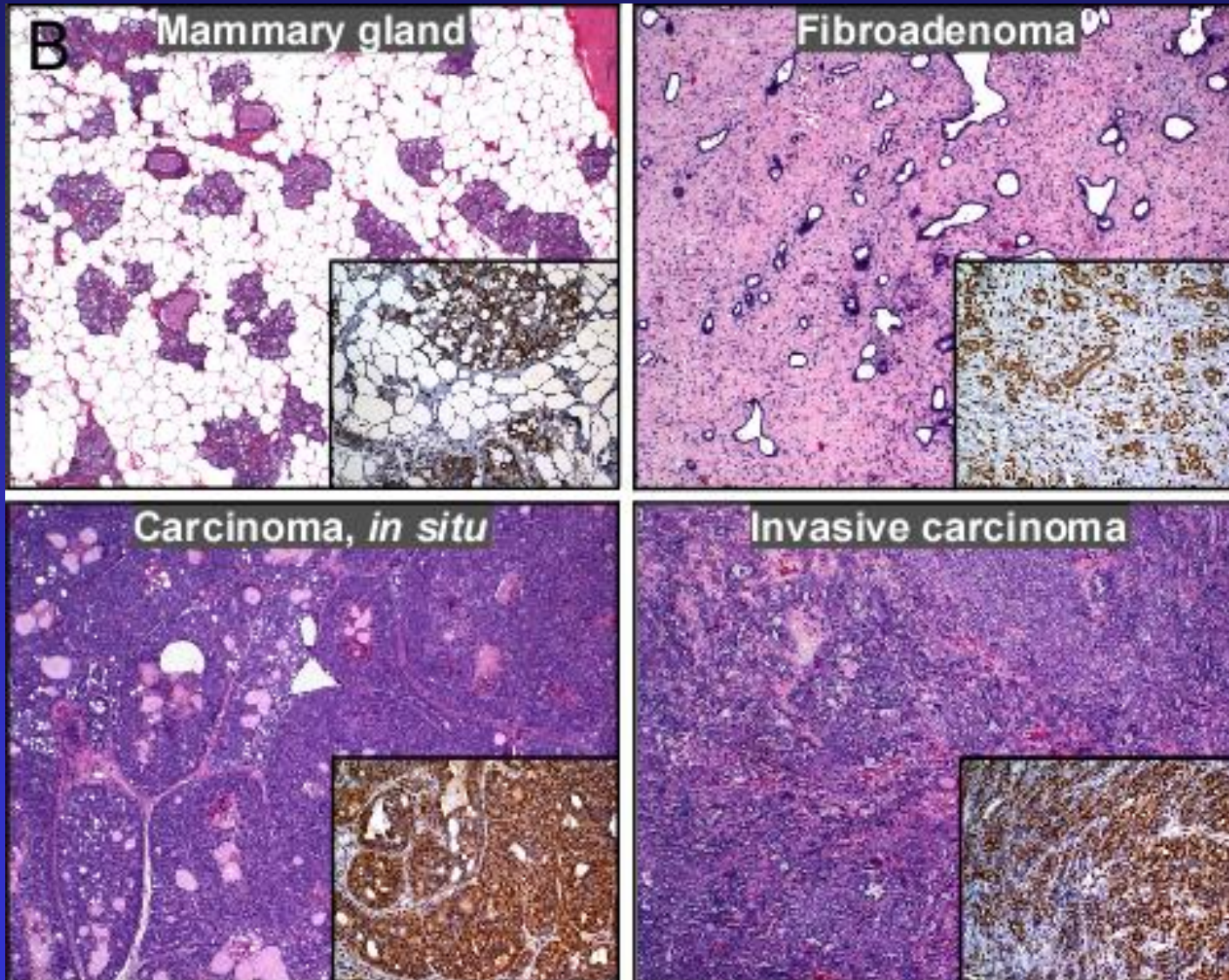


■ Group
□ Isolated

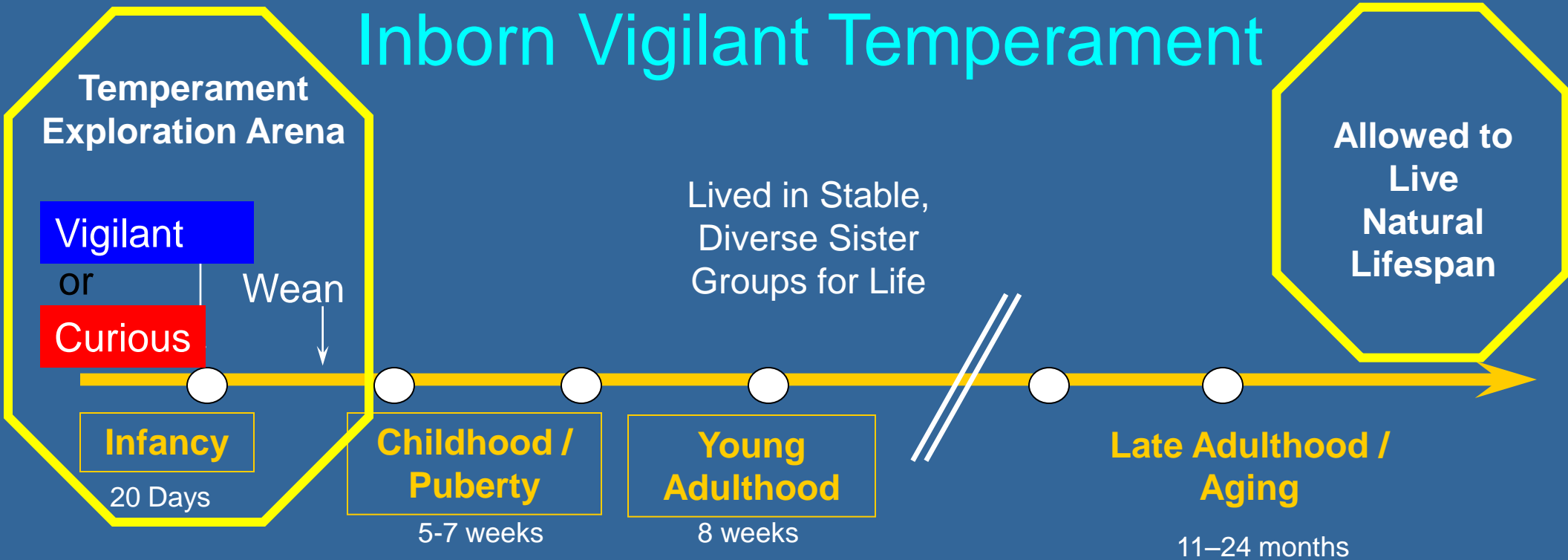
Hormonal Stress Response During Middle Age



Glucocorticoid Receptors (brown) In Rat Mammary Glands And Spontaneous Tumors



Inborn Vigilant Temperament



DEVELOPMENTAL APPROACH
Same environment, inborn diffs



Cavigelli

Inborn Vigilant Temperament

Temperament
Exploration Arena

Vigilant

or

Curious

Wean

Infancy

20 Days

Childhood /
Puberty

5-7 weeks

Young
Adulthood

8 weeks

Late Adulthood /
Aging

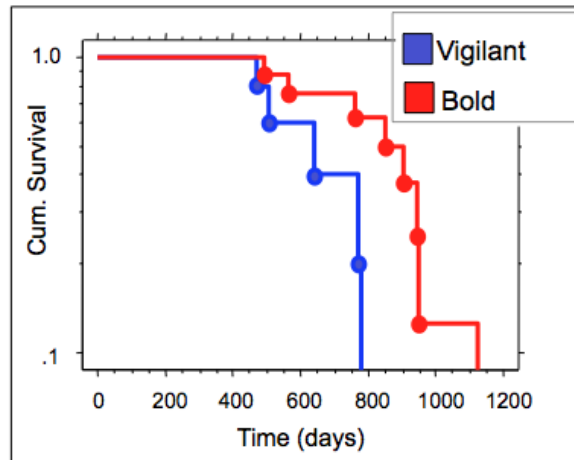
11-24 months

Allowed to
Live
Natural
Lifespan

Lived in Stable,
Diverse Sister
Groups for Life



Mammary Tumor



$\chi^2 = 4.04, p = .045$



Cavigelli

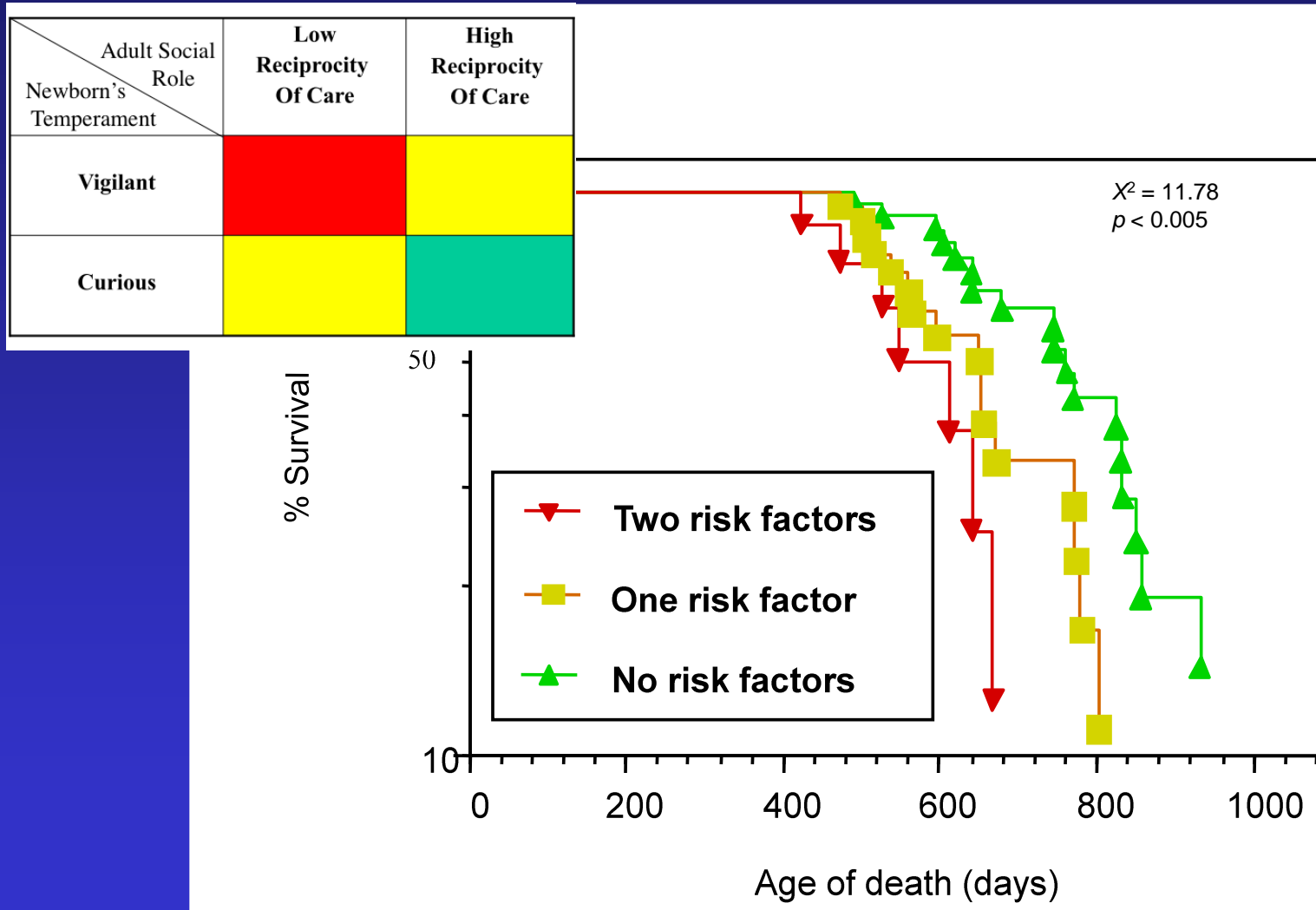
Vigilance and Social Roles: Two Additive Psychosocial Risk Factors For Survival

Adult Social Role Newborn's Temperament	Low Reciprocity Of Care	High Reciprocity Of Care
Vigilant		
Curious		

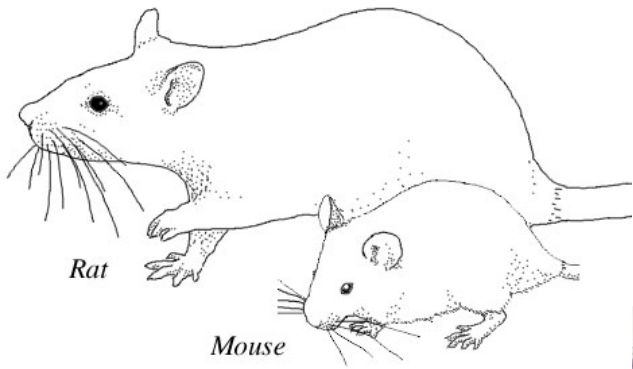
**Reciprocity of Care
“Tend and Befriend”
During Everyday Stressors**



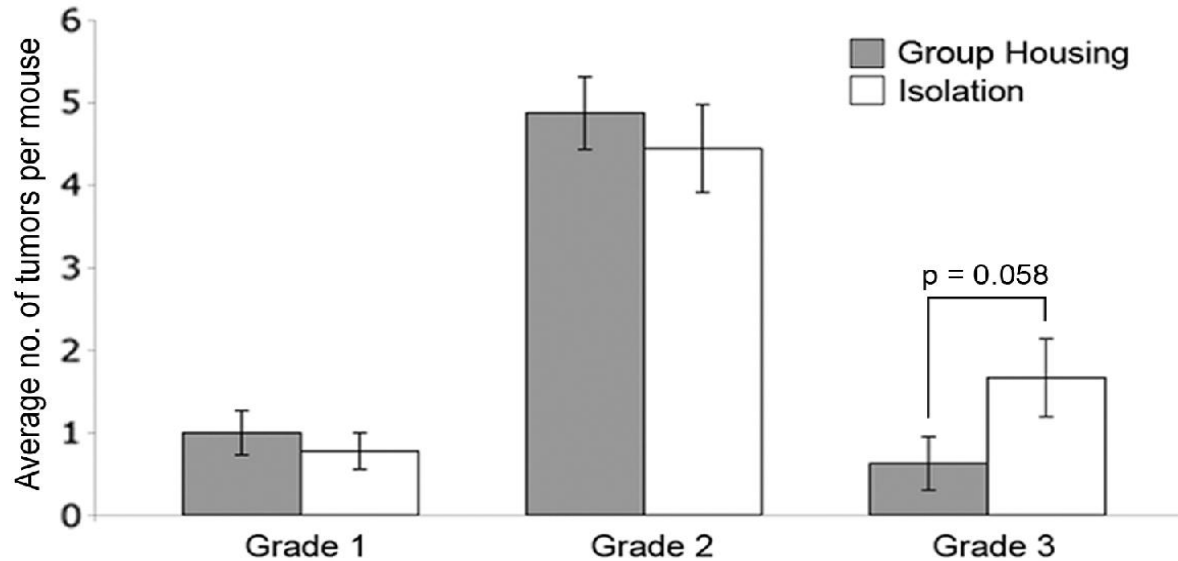
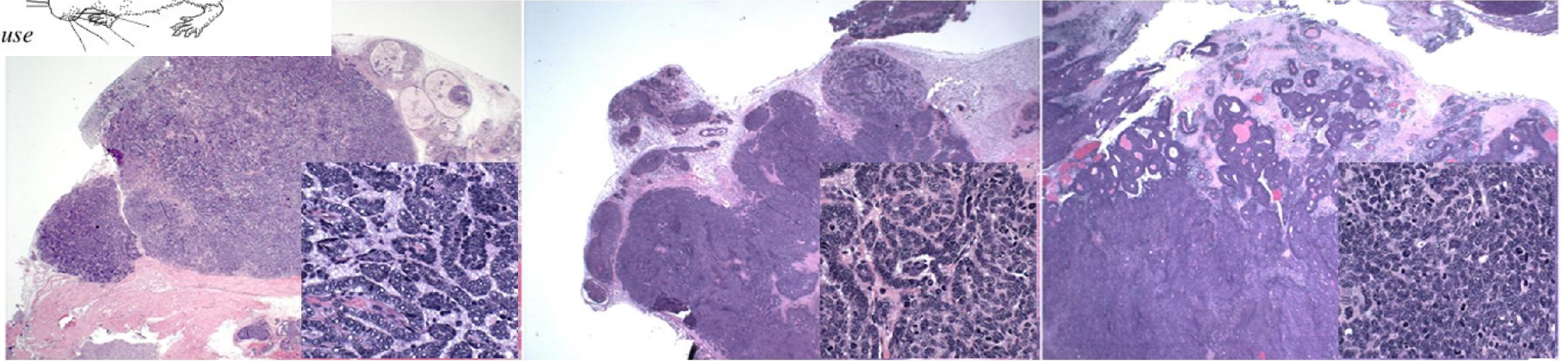
Vigilance and Social Role: Two Additive Psychosocial Risk Factors For Survival



C3(1) SV40 Tag transgenic mice (simian virus)

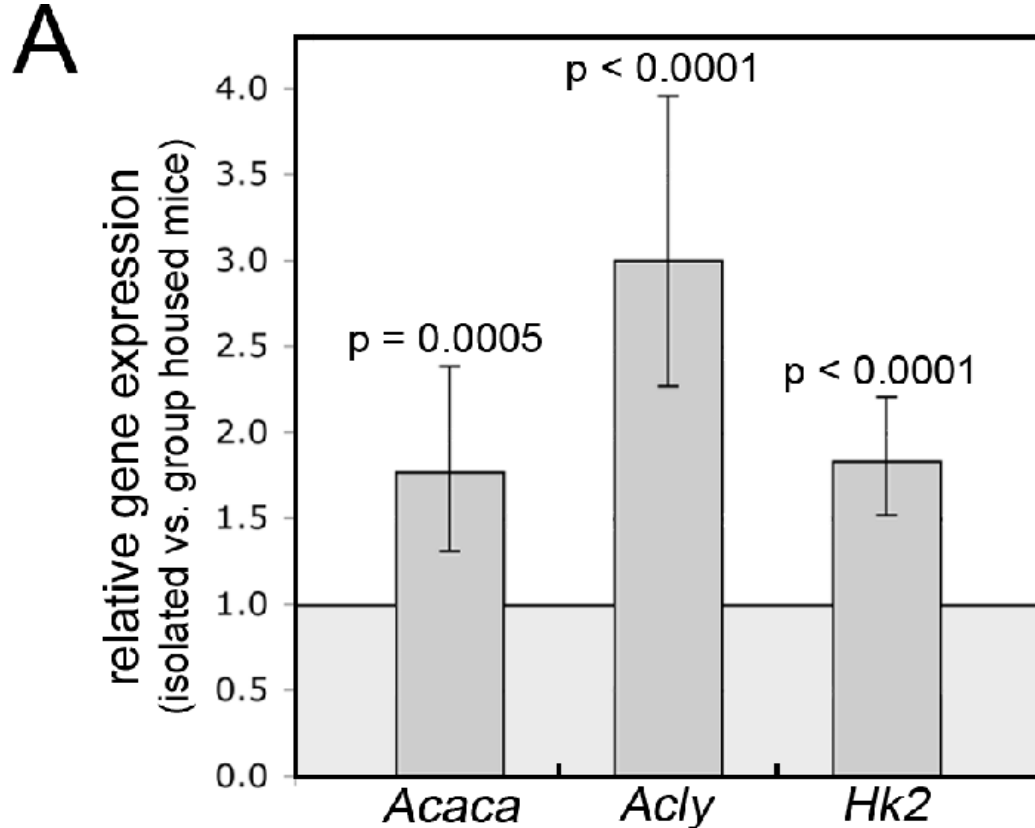


Invasive
Carcinoma
(23 weeks)

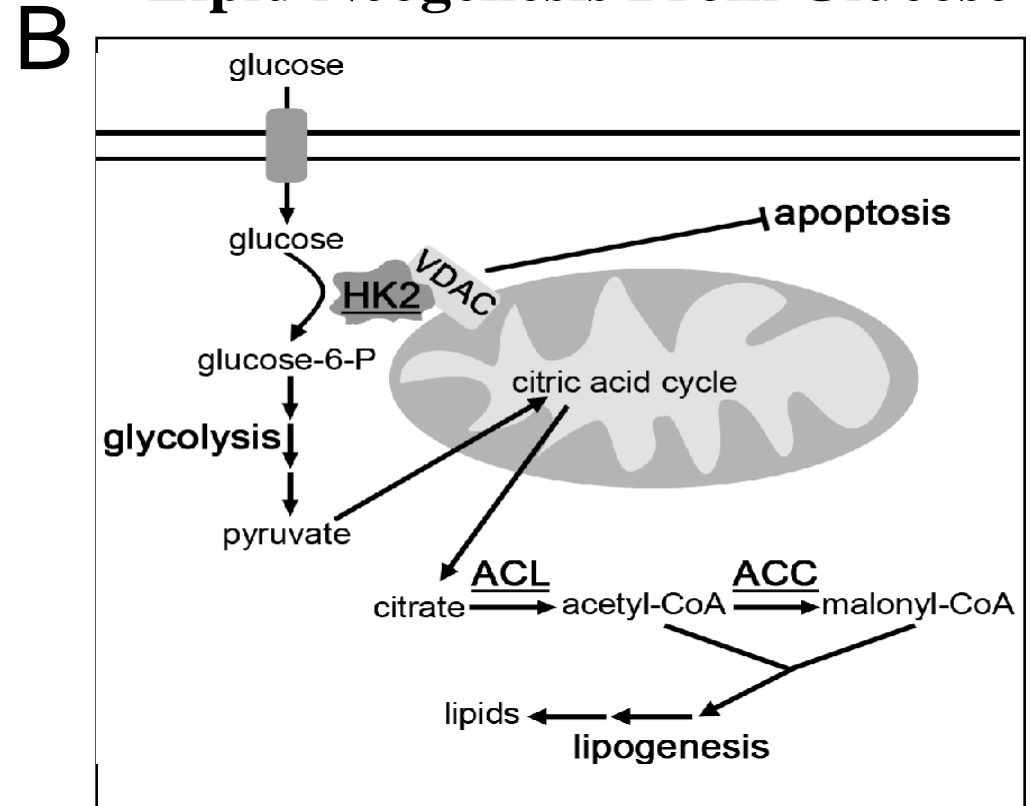


Relatively *increased* expression of key lipid synthesis genes in mammary gland tissue from isolated mice

3 upregulated genes



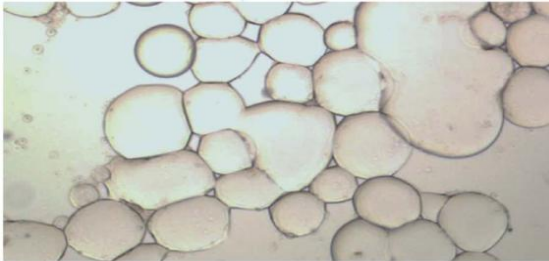
Lipid Neogenesis From Glucose



Glucocorticoid stress - lipid metabolism connection

Where??

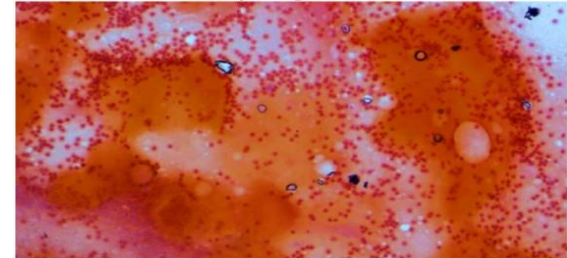
Mammary Adipocyte
Fraction



Mammary Fat Pad

“Soil”

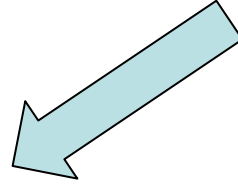
Mammary Non-Adipocyte Fraction



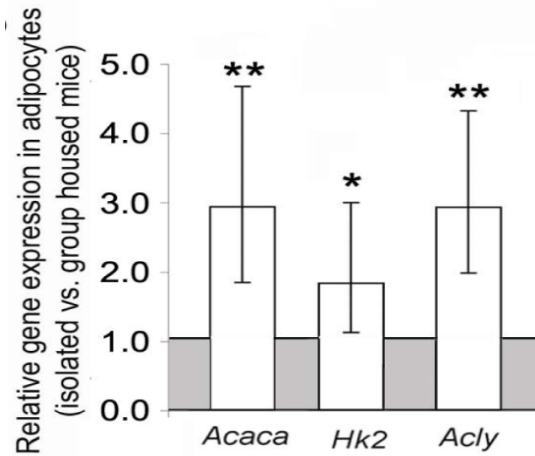
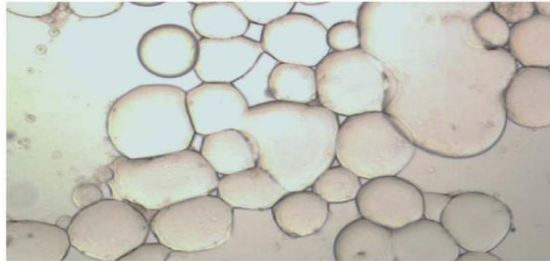
**Epithelial Ducts
Stroma**

“Seed”

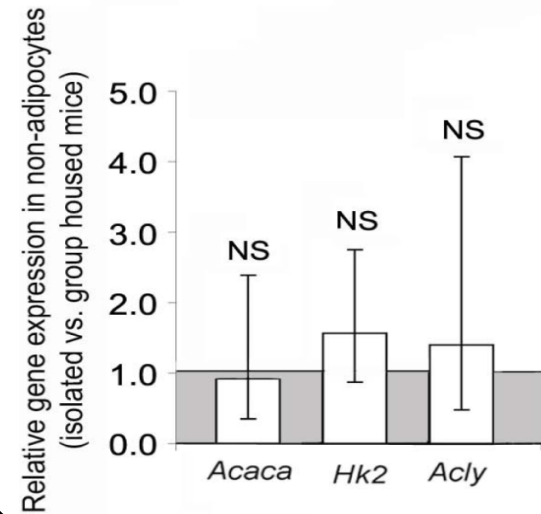
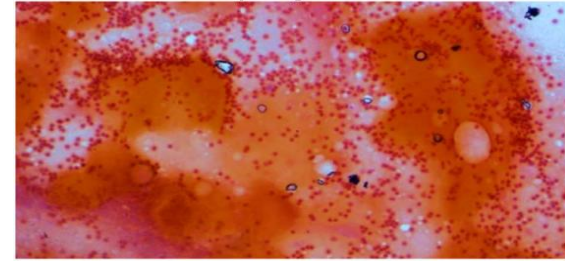
Stress-lipid metabolism connection



Mammary Adipocyte Fraction

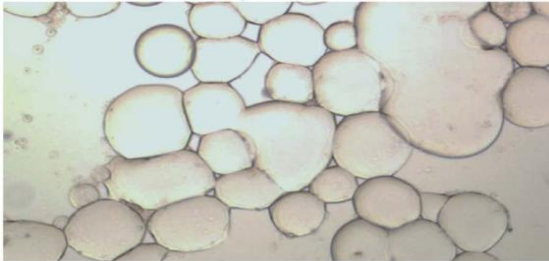


Mammary Non-Adipocyte Fraction



Stress-lipid metabolism connection Specific To Mammary Gland??

Mammary Adipocyte
Fraction



Mammary Fat Pad

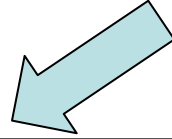
“Soil”

Visceral Gonadal Fat

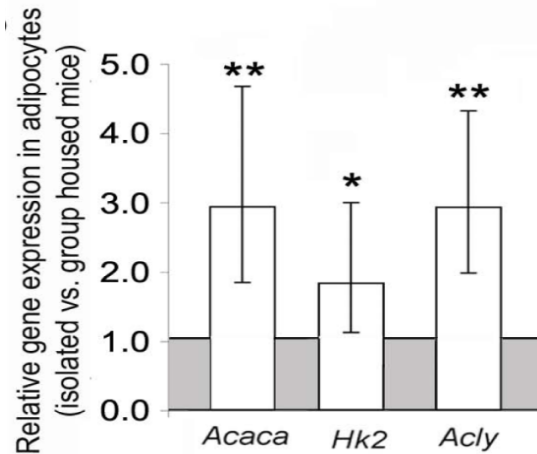
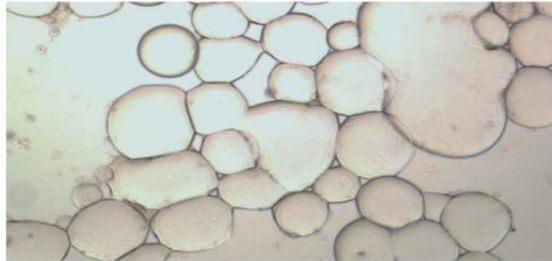


**Ovarian Uterine
Fat Pad**

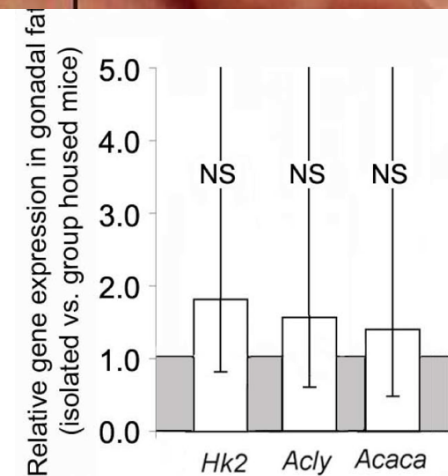
Stress-lipid metabolism connection Specific To Mammary Gland



Mammary Adipocyte Fraction



Visceral Gonadal Fat



SUMMARY OF CONTRAST WITH EXPOSOME APPROACH

**Unique contributions of ethology approach to
Molecular mechanisms of cancer**

AND

Effective Targeted Therapies

Setting up, but not pre-empting Conzen final presentation