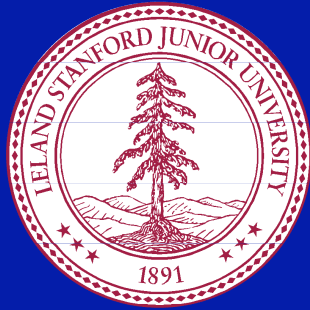
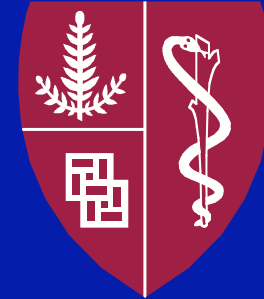


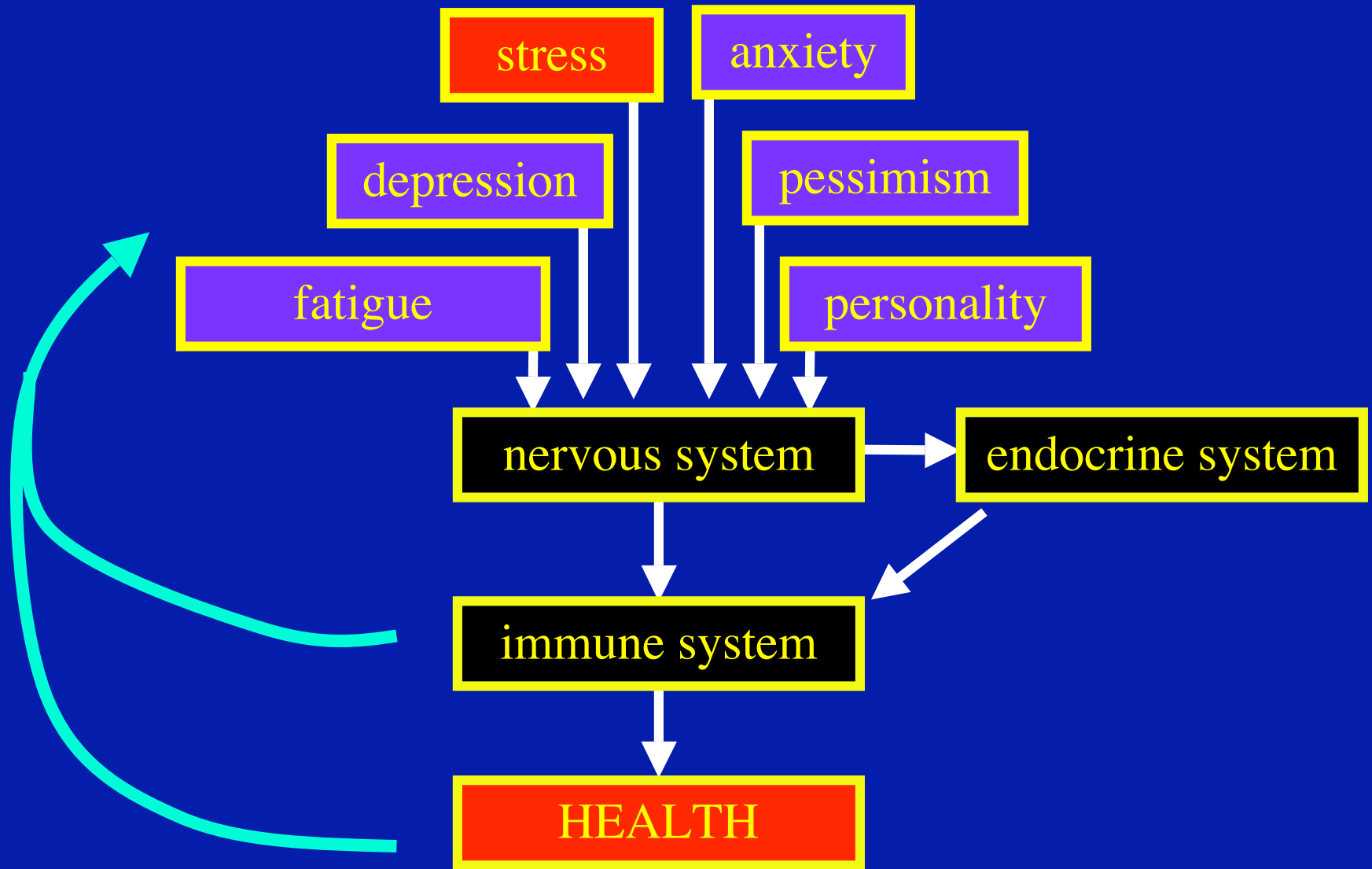
A Hassle A Day May Keep The Doctor Away: Stress & The Augmentation of Immune Function



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Psycho-Neuro-Immunology (PNI)



STRESS

Stress can be defined as a cluster of events that begins with a stimulus (**stressor**), precipitates a reaction in the brain (**stress perception**), and subsequently results in the activation of fight / flight systems in the body (**stress response**).

Acute stress = minutes to hours

Chronic stress = weeks to months to years &
dysregulation of diurnal rhythm

(Dhabhar & McEwen, Brain Behavior & Immunity, 1997, 11: 286.)

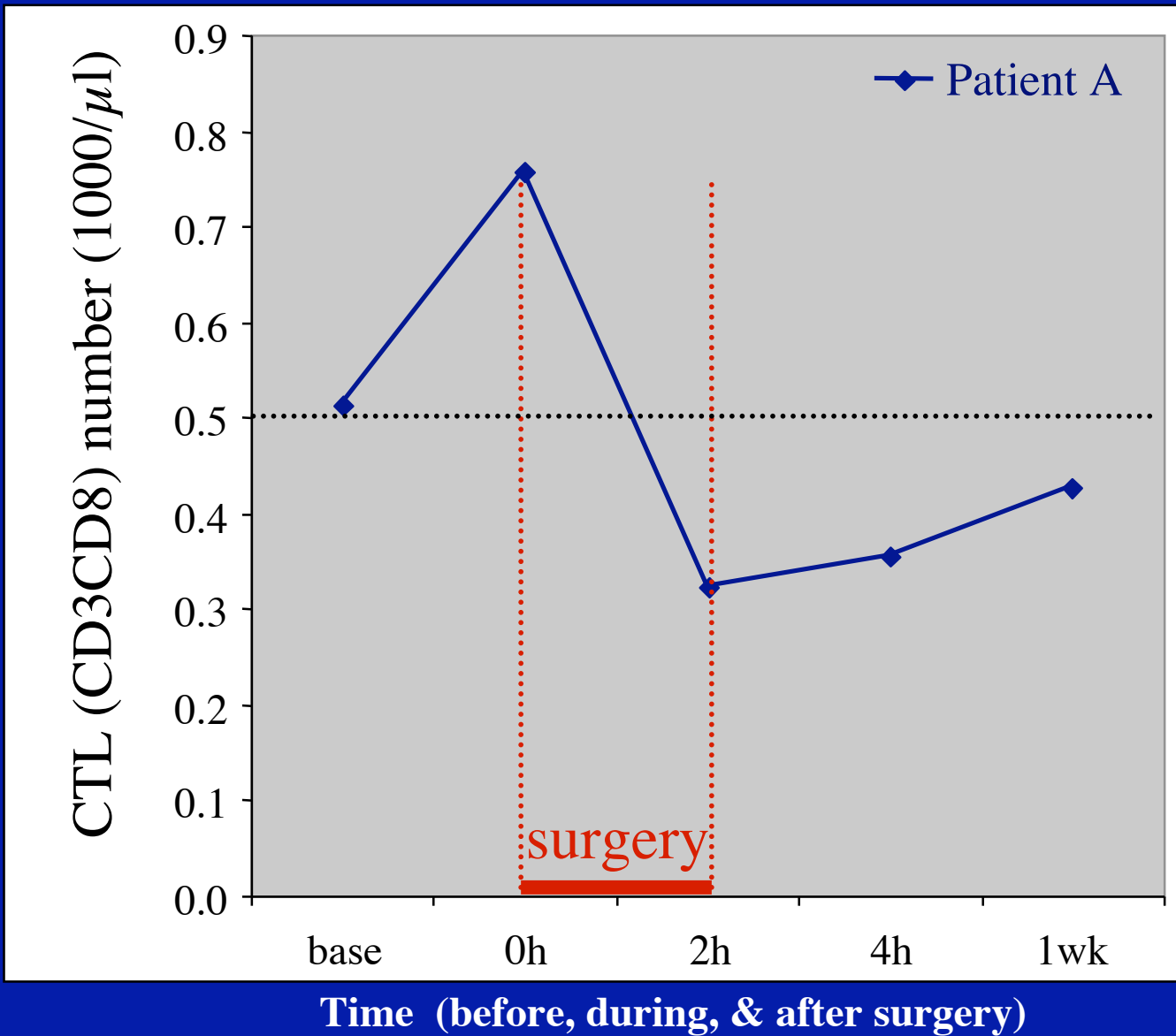
- Most biomedical research is focused on pathogens & disease
- While my laboratory also studies disease, our main emphasis is on understanding the biological mechanisms that maintain or restore HEALTH
- The following presentation will suggest that the acute/short-term, fight-or-flight stress response is nature's fundamental survival system and one of its principal health-promoting mechanisms

Our Initial Hypothesis: Just as the stress response prepares the **cardiovascular, musculoskeletal, and neuroendocrine** systems for fight or flight, under some conditions, it may also prepare the **immune** system for challenges (wounding or infection) that may be imposed by a stressor (predator)
(Brain, Behavior, & Immunity, 1994)

*Short-term stressors will **ENHANCE** immune function within compartments (e.g. skin) that are likely to be compromised by the actions of a “stressor” (e.g. predator, surgery)...*

Q: What happens to immune cell numbers in the blood during acute / short-term stress?

Surgery stress induced changes in blood leukocyte numbers



Collaboration with: Ickovics, Jokl, Rosenberger, Fulkerson, & colleagues, Yale; & Epel (UCSF)

Similar redistribution patterns seen during stress in mouse, rat, horse, monkey, and other species...

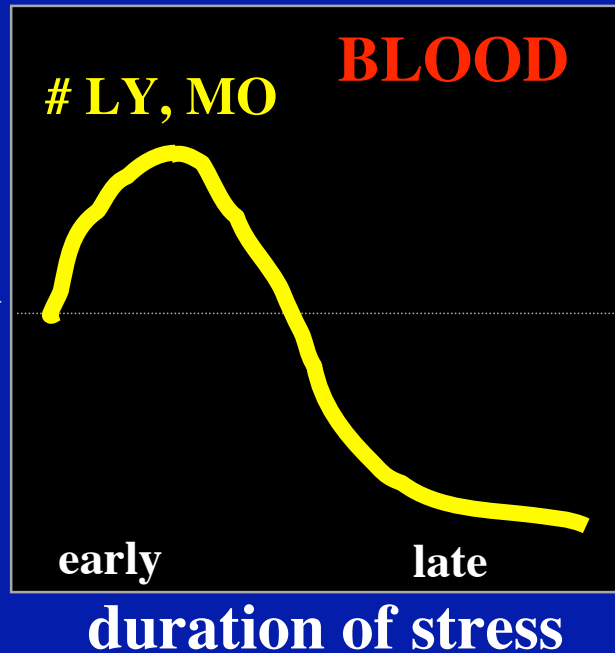
Integrated Model

BARRACKS → **BOULEVARDS** → **BATTLE STATIONS**

spleen

marginated pool

bone marrow?



skin

lymph nodes

hormones?

genes & proteins?

functional consequences?

clinical ramifications?

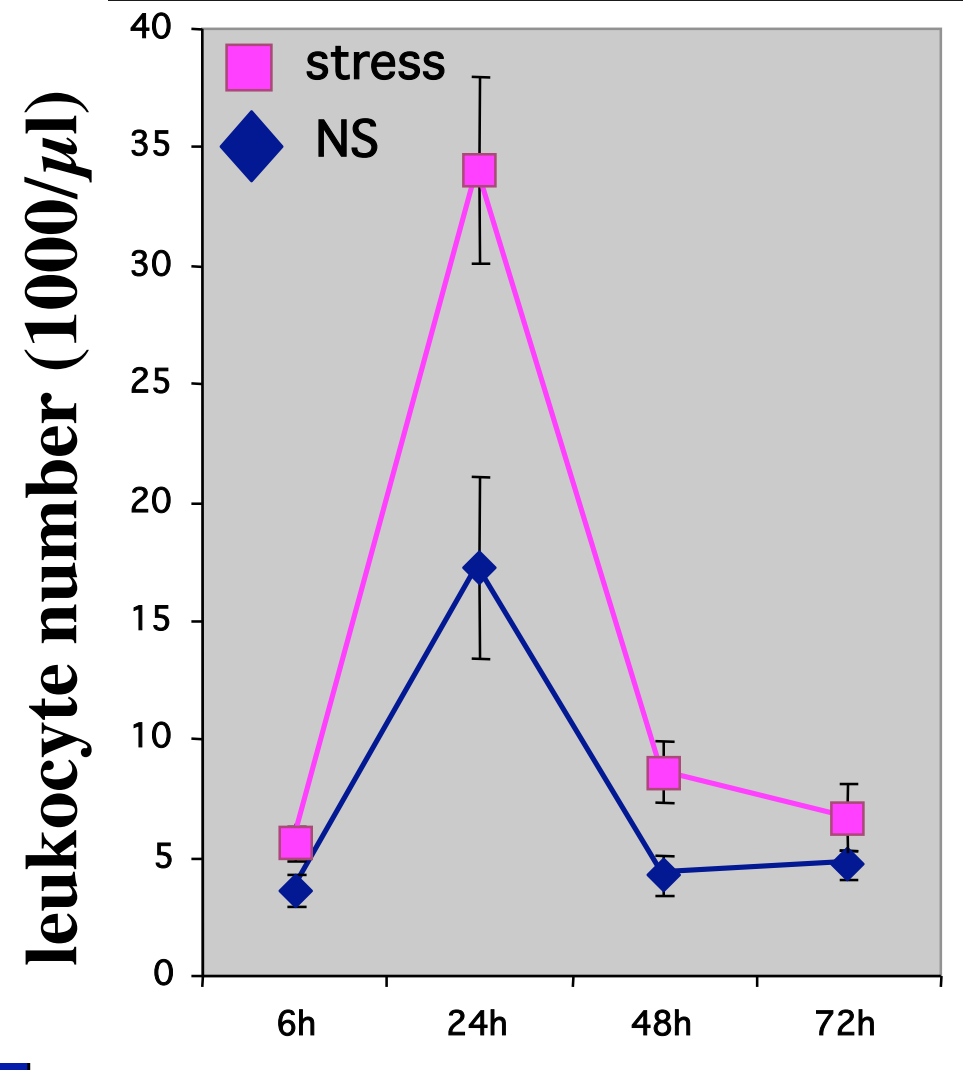
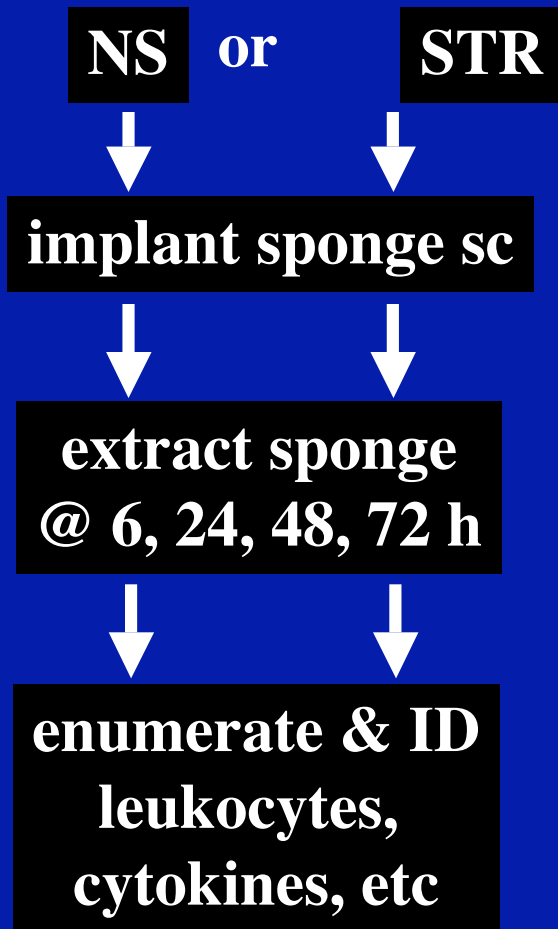
Efficient wound healing requires rapid leukocyte infiltration into a wound site

Q: Can acute stress experienced at the time of wounding/surgery accelerate the rate of leukocyte entry at the site of wounding/surgery?

Does acute stress ↑ leukocyte traffic to a site of surgery?

Absorbable Surgical Sponge

- hemostatic plug
- repair wound cavities, ear drums, tooth extraction sockets
- “filler” in some surgical procedures



Finding: Acute stress increases immune cell traffic into a site of immune activation

Q: Does this increase the magnitude/robustness of the ensuing immune response?

A: Yes (J Immunol, 1996; PNAS 1999, 2000)

Implication: Harness acute stress physiology to enhance vaccine efficacy...

Hypothesis: Mice that are acutely stressed before primary immunization will show higher numbers of memory cells in sentinel lymph nodes

Time Line Of Experiment

No Stress

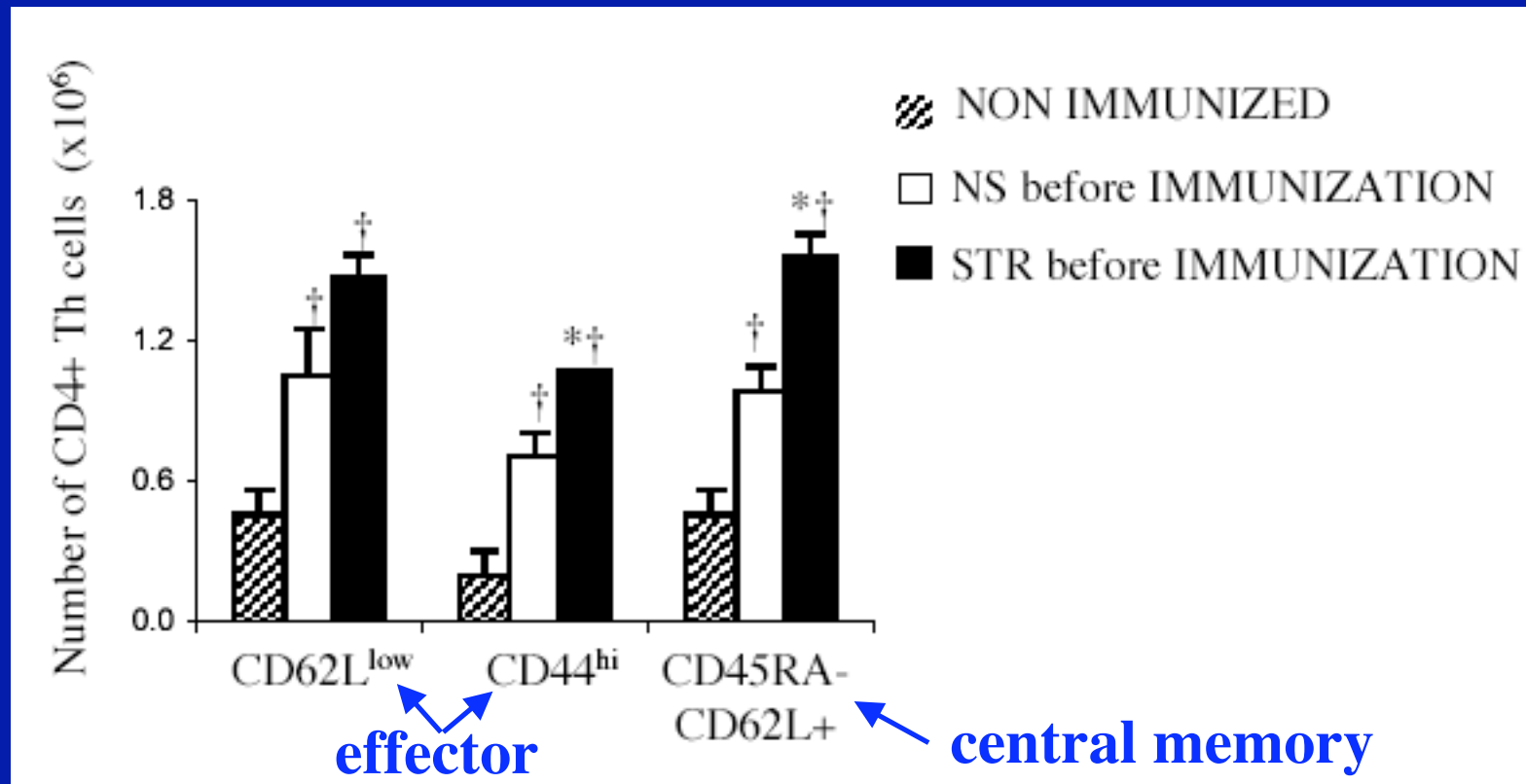
Acute Stress

immunize with model
vaccine antigen (KLH)

1 week

quantify memory T cells in sentinel lymph nodes

Acute stress ↑↑ memory T cells in sentinel lymph nodes



Implication: ↑↑ memory for the immunizing antigen

Hypothesis: Mice that were acutely stressed at the time of primary immunization will show an enhanced immune response upon antigen re-exposure months later

Time Line Of Follow-up Experiment

No Stress

Acute Stress

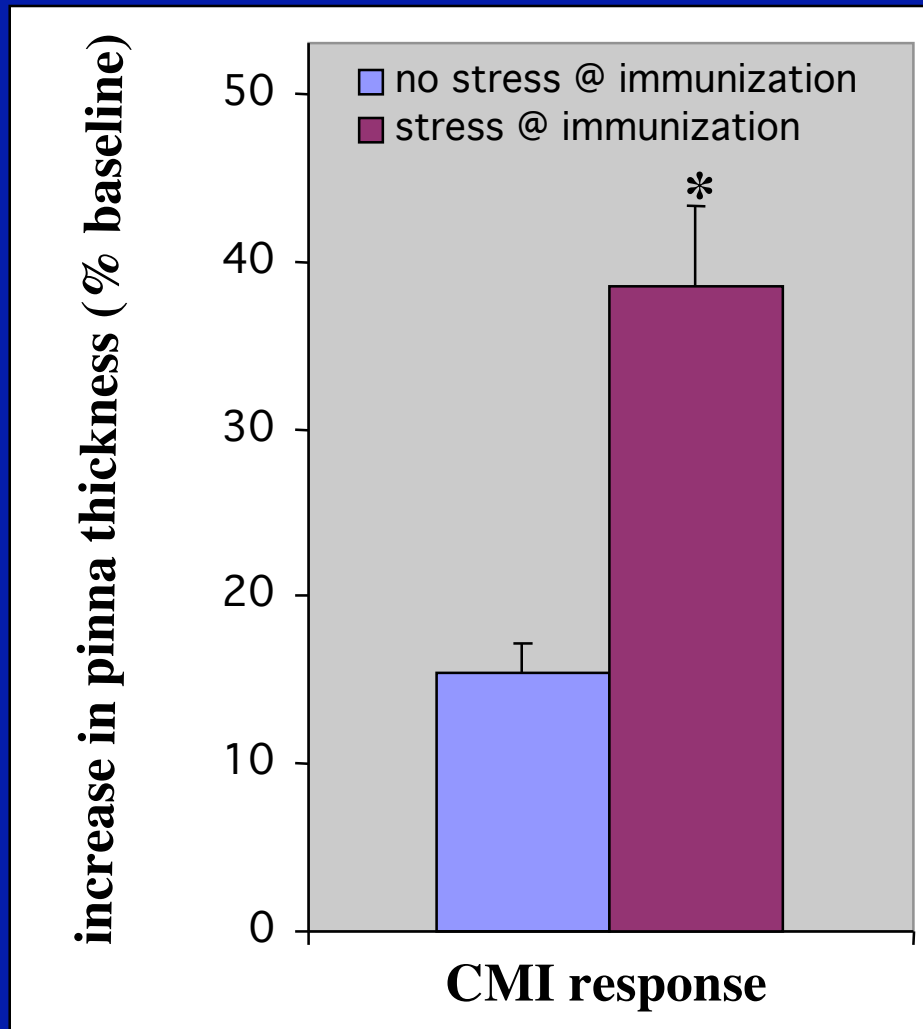
immunize with model
vaccine antigen (KLH)

9 months!!!

re-expose to antigen at novel site (mimics infection)

quantify immune response

Acute stress at primary immunization enhances a secondary immune response **9 months later**

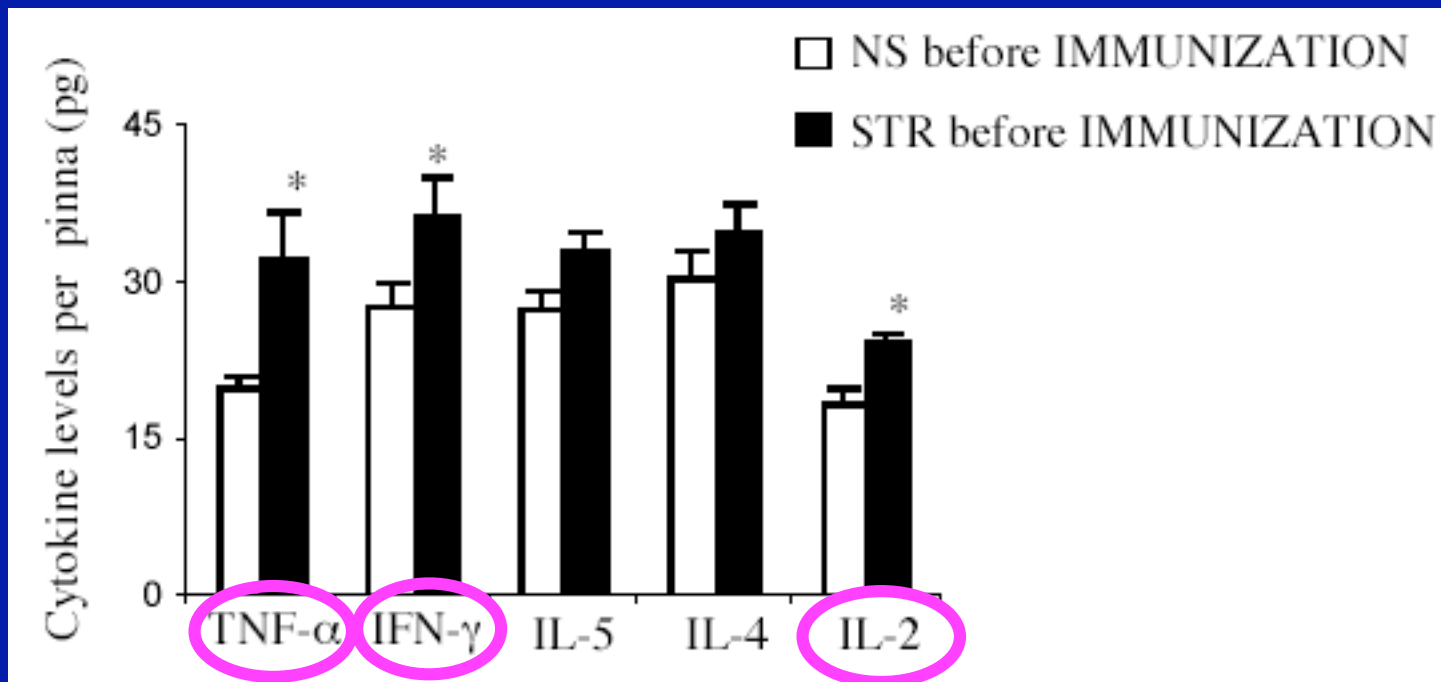


Implication:

↑↑ effector function

↑↑ protection

Acute stress before primary immunization ↑↑ Type 1 cytokine levels at site of secondary immune response 9 months later



Implication: ↑↑ effector function, ↑↑ protection

Immune activation (wounding, surgery, vaccination)
invariably induces a stress response

Natural stressors (aggression, predation, accidents)
invariably activate the immune system

The acute stress response may act as a natural,
endogenous adjuvant that boosts immune responses
that are coupled with stress

Some individuals mount robust, adaptive, acute stress responses, but others may not

In many clinical situations (vaccination, surgery, infection, cancer), we may need to turn this response **ON** to **enhance protective immunity**

In patients with proinflammatory or autoimmune disease, we need to turn this response **OFF** to **inhibit exacerbation of pathological immune reactions**

Q: What are the **hormones** that mediate an acute stress induced enhancement of skin immune function?

A: Epinephrine (1-24 h) & corticosterone (24 h...)

Dhabhar & McEwen, 1999, PNAS, 96: 1059

Clinical Relevance of Acute Stress Induced Leukocyte Redistribution

Study: Acute Stress & Recovery From Knee Surgery

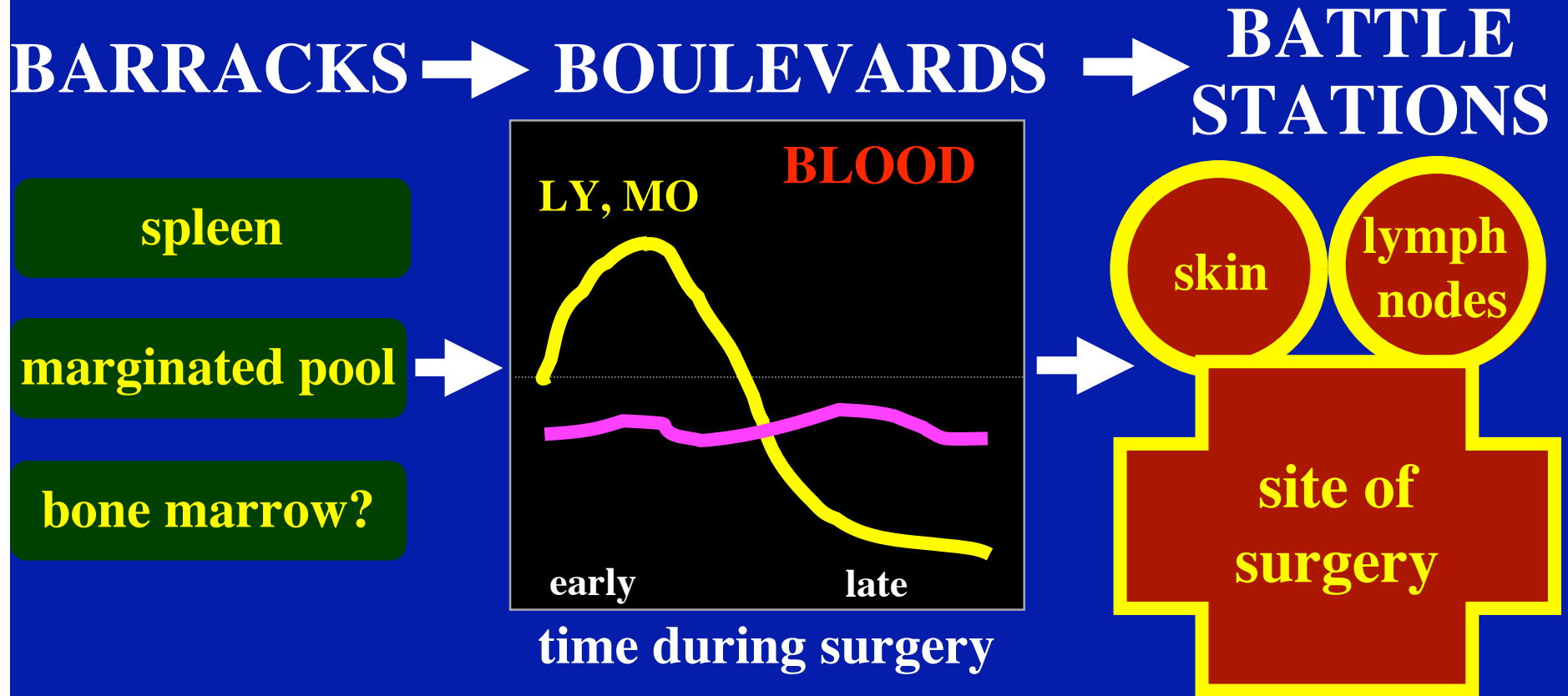
Aim 1: Identify blood leukocyte redistribution profiles of patients undergoing knee surgery (meniscal repair, ACL reconstruction)

Aim 2: Examine whether profiles predict recovery

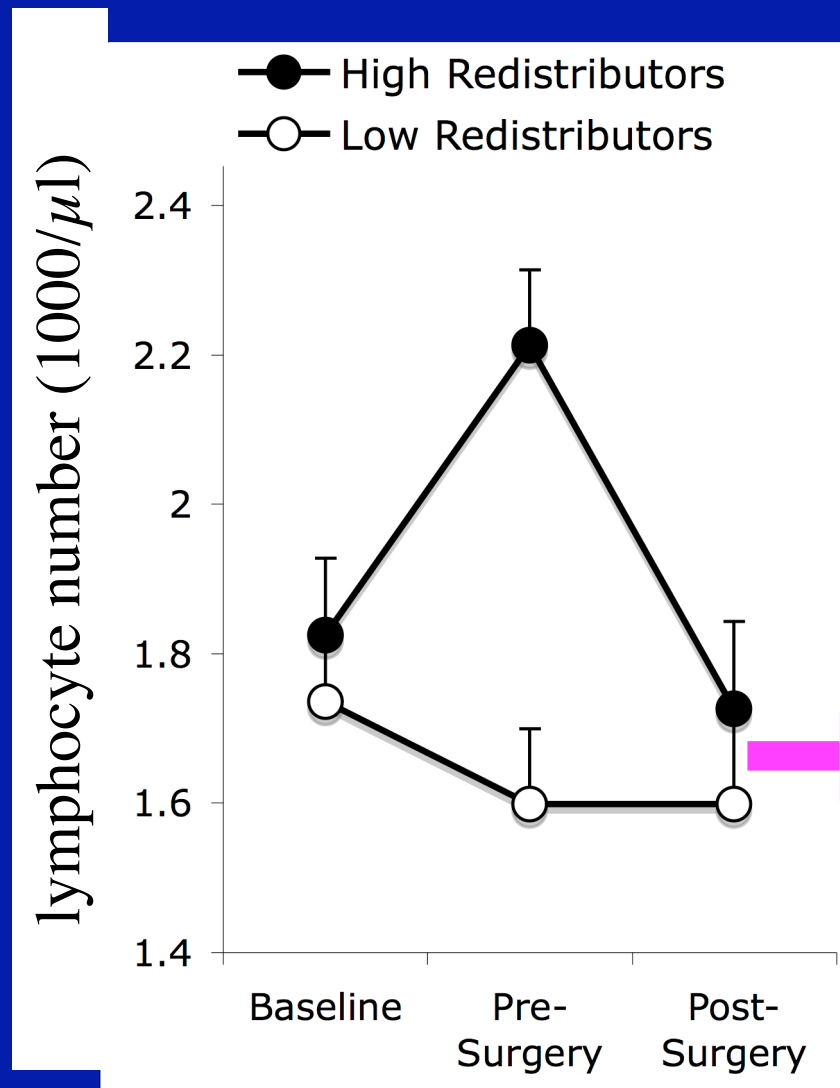
Hypothesis: “Adaptive” leukocyte redistribution during surgery will predict/mediate enhanced recovery

Collaboration with: Ickovics, Jokl, Rosenberger, Fulkerson, & colleagues, Yale; & Epel (UCSF)

A priori definition of “adaptive” leukocyte redistribution during stress of surgery:



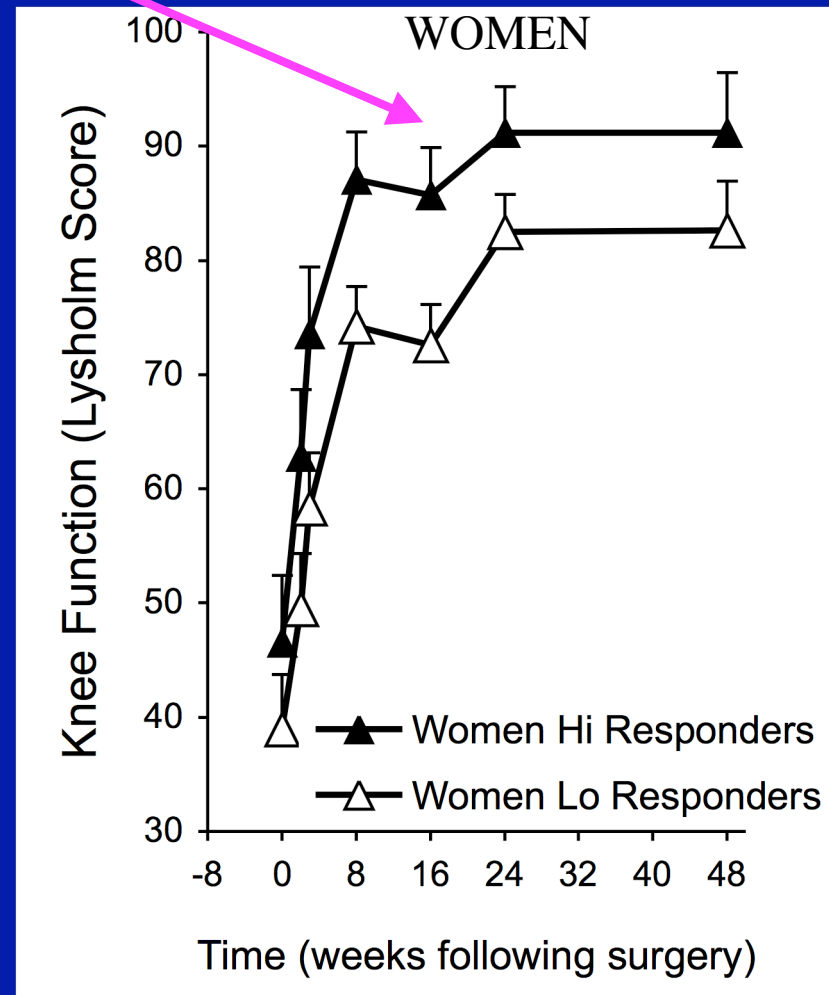
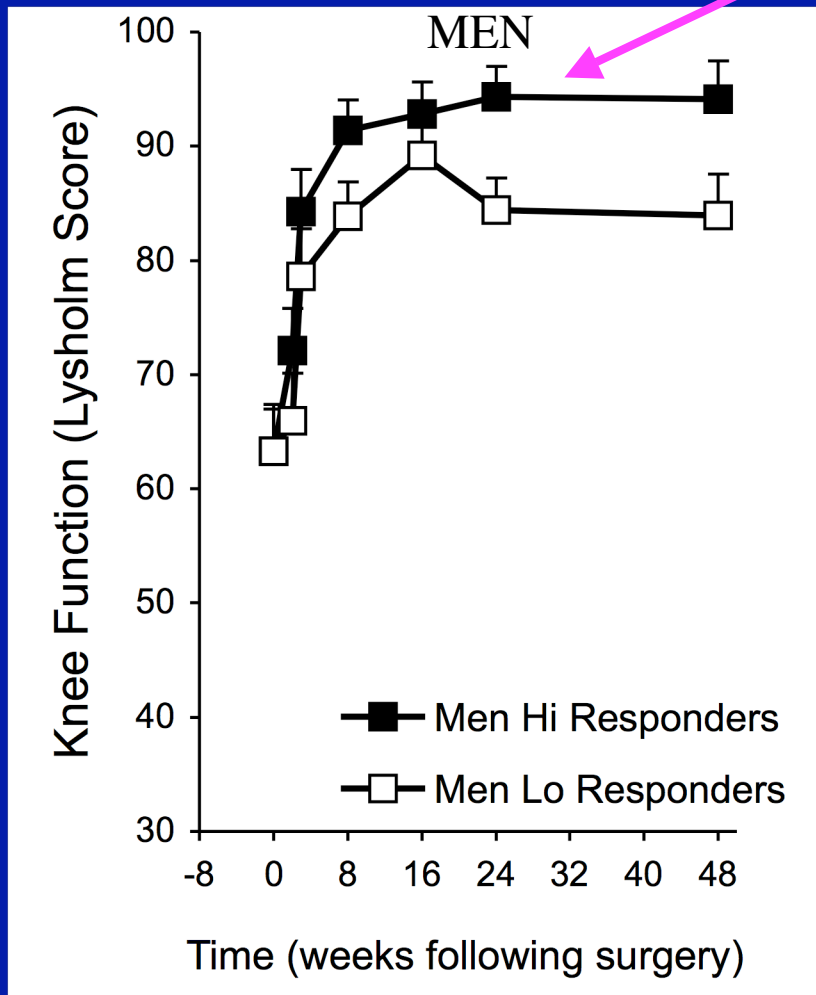
Some patients show “adaptive” leukocyte redistribution during surgery stress, others do not...



Can these differences predict recovery?

High redistributors show enhanced recovery

patients who showed adaptive redistribution



Goals:

- Identify low versus high responders before patient goes in for surgery
- Identify factors mediating gender differences
- Design behavioral and pharmacological interventions to put low responders into high responder state during surgery

STRESS PHYSIOLOGY
↑ IMMUNE FUNCTION

BENEFICIAL:

wound healing
vaccination
infection
cancer?

HARMFUL:

psoriasis, dermatitis,
asthma, IBD,
inflammatory,
autoimmune,
cardiovascular disease,

elucidate mechanisms...
...translate to clinic...

What about stress & immunosuppression?

The Stress-Immune Spectrum



ACUTE / EUSTRESS

- brief (0.5 - 2.5 h)
- normal circadian rhythm
- adaptive response
- ↑ leukocyte mobilization
- ↑ immune responses

J Immunology, 95, 96a,b

PNAS, 00, 02, 05

Am J Psychiatry, 03

Am J Physiology, 05; Int Imm 05

CHRONIC / DISTRESS

- long (wks, mns, yrs)
- dysregulated rhythm
- maladaptive response
- ↓ leuko base & mobilizn
- ↓ protective immune resp
- ↑ dysregulation

BBI, 97, 02; Neuroendocrinol, 97

PNAS, 99, 04

JNCI, 05; J Proteome Res, 07

Overall Conclusion:

Acute stress directs immune cell traffic to potential “battle stations” in the body, enhances immune cell function, and augments **primary (innate)**, and **secondary (adaptive)** immune responses

We need to study, and clinically harness, the acute stress survival response, that evolution has already finely chiseled and sculpted, just as much as we study its maladaptive ramification (chronic stress) that evolution yet has to catch up with...

(Dhabhar, Abelson Seminar, AAAS, 2008)

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