

## Fisiopatologia da febre



High fever, by Mats Eriksson

**Alexandre A. Steiner**  
 Professor Associado  
 Departamento de Imunologia  
 Instituto de Ciências Biomédicas  
 Universidade de São Paulo



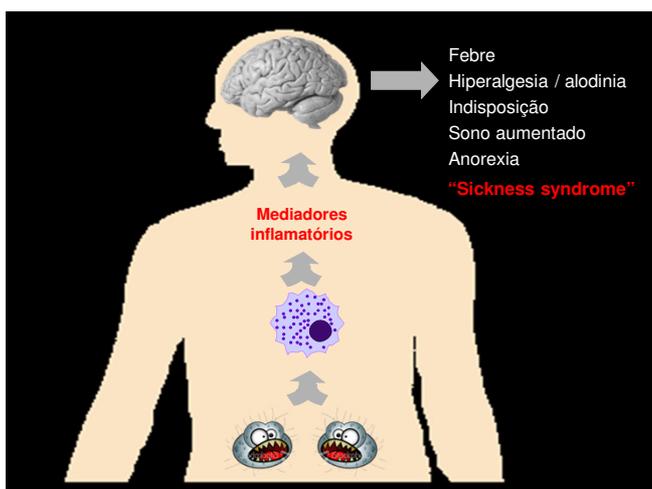
Robert Dantzer

"Anyone who has experienced a viral or bacterial infection knows what it means to feel sick... (But) despite their impact on well-being, the symptoms of sickness are usually ignored."



Benjamin Hart

"The behavior of sick animals and people is not a maladaptive response or the effect of debilitation, but rather an organized, evolved behavioral strategy to combat viral and bacterial infections."



### ROADMAP



- 1) Historical highlights
- 2) Mechanisms of fever induction
- 3) Impacts of fever on host defense: approaches
- 4) Impacts of fever on host defense: mechanisms & therapy
- 5) Hypothermia as an alternative host defense strategy

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### THE OLDEST MEDICAL RECORD OF FEVER IN HUMAN CIVILIZATION



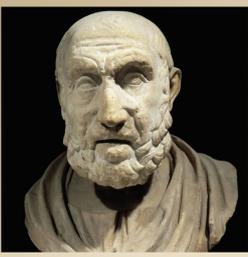
"Feeble pulse and fever are associated with hopeless injuries and deafness..."

Ancient civilizations tended to view fever as being induced by evil spirits.

Edwin Smith Papyrus

1700 BC Present day

### HIPPOCRATES OF KOS



Precise descriptions of febrile diseases:

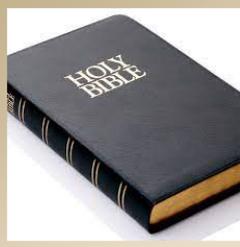
- Sustained fevers of pneumonia
- Intermittent fevers of malaria
- Stepwise rise in temperature in typhoid fever

Observations were made long before the advent of the clinical thermometer.

Fever caused by an excess of yellow bile which, like fire, was hot and dry.

Believed in the beneficial effects of fever.

400 BC Present day



In the Old Testament, fever was part of God's punishment for sins.



THE FIRST BOOK OF MOSES, CALLED GENESIS.

CHAPTER I.

When God created the earth, the earth was without form, and void, and darkness was upon the face of the deep, and the spirit of God hovered over the waters.

100 BC Present day



Embellished Hippocrates' humoral theory.

Prevailing medical thinking until 1.700 AD.

But belief that fever could be beneficial was gone.



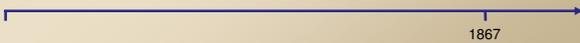
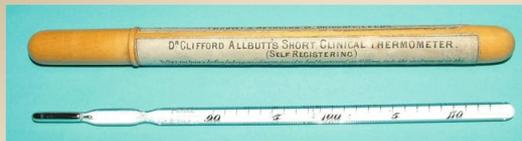
**LEECHES: AN EARLY NINETEENTH-CENTURY OBSESSION**



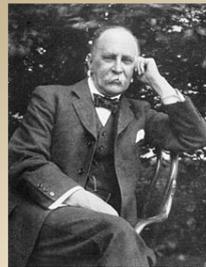
Led by François Broussais, physicians thought claimed that all fevers were caused by inflammation of the organs, and that leeches could be used to treat these fevers by removing blood from the parts of the skin closest to the affiliated organs.



**FIRST CLINICAL THERMOMETER TO BECOME COMMERCIALY AVAILABLE**

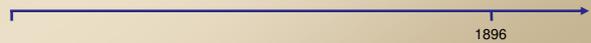


**WILLIAM OSLER**



"Humanity has but three great enemies: fever, famine, and war; of these by far the greatest, by far the most terrible, is fever."

(in the 47th annual meeting of the American Medical Association)



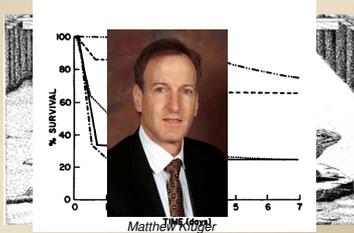


**PRIMEIRA EVIDÊNCIA DIRETA DO VALOR DA FEBRE**

**Fever and Survival**

SCIENCE, VOL. 188  
4 November 1974; revised 8 January 1975

MATTHEW J. KLUGER  
Department of Physiology, University of Michigan Medical School, Ann Arbor 48104  
DANIEL H. RINGLER  
MIRIAM R. ANVER  
Unit for Laboratory Animal Medicine, University of Michigan Medical School



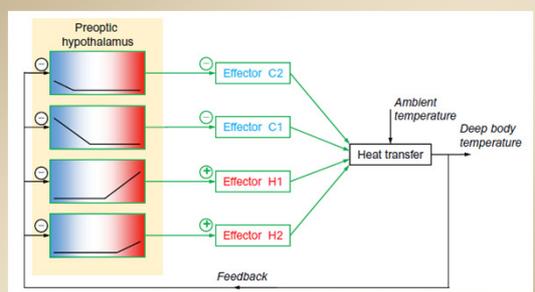
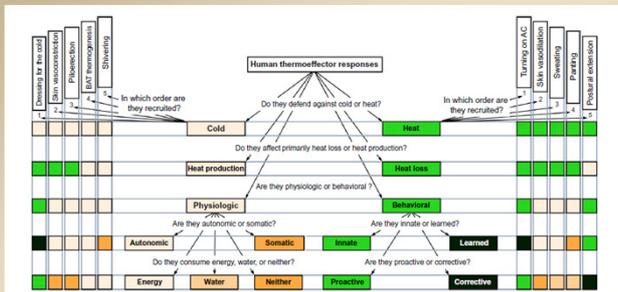
Matthew Kluger

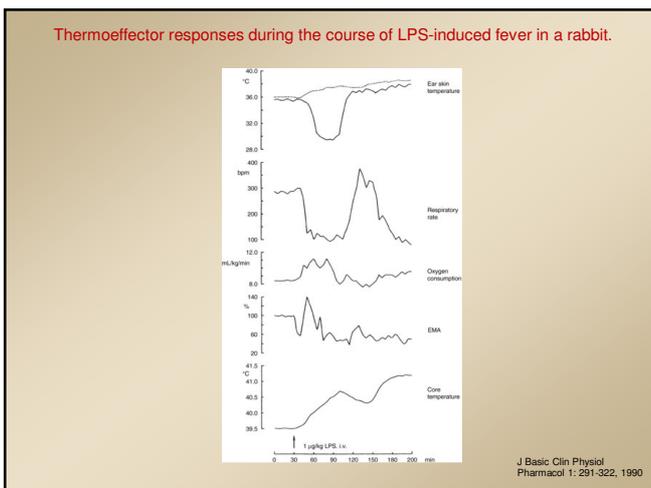
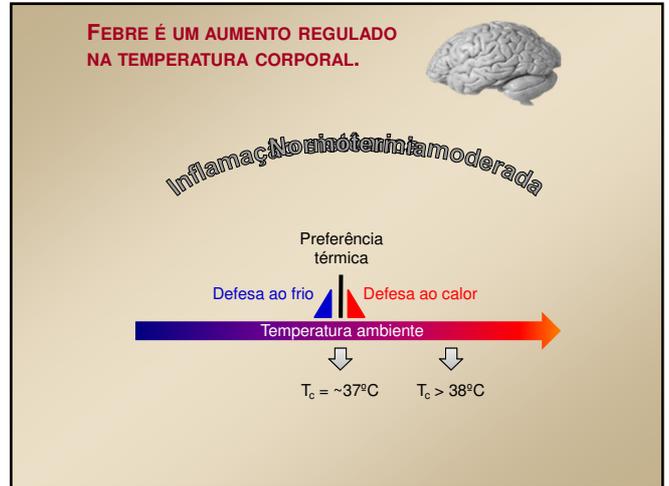
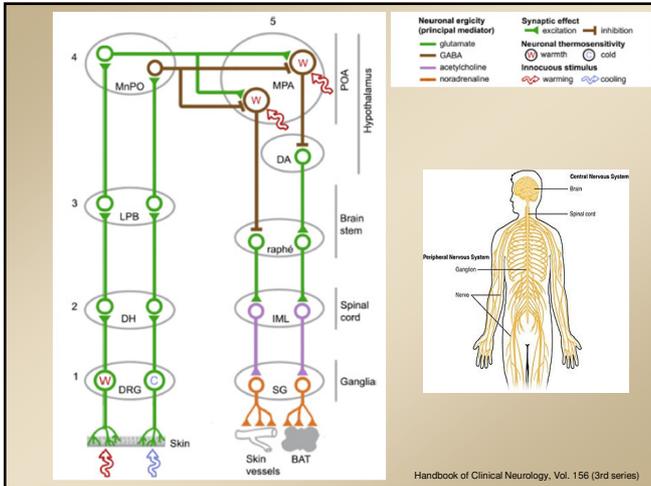
1975

**ROADMAP**



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**THE DISCOVERY OF THE ENDOGENOUS PYROGENS**

**STUDIES ON THE PATHOGENESIS OF FEVER**  
 II. IDENTIFICATION OF AN ENDOGENOUS PYROGEN IN THE BLOOD STREAM FOLLOWING THE INJECTION OF TYPHOID VACCINE\*

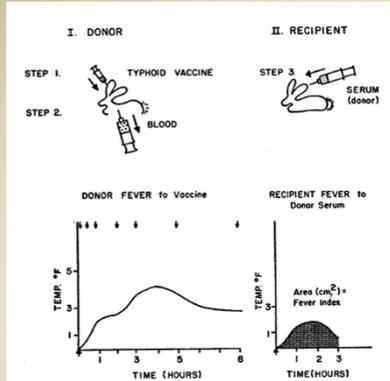
By ELISHA ATKINS,† M.D., AND W. BARRY WOOD, JR.,§ M.D.  
 (From the Department of Medicine, Washington University School of Medicine, and the Barnes and Wohl Hospitals, St. Louis)

(Received for publication, July 7, 1955)

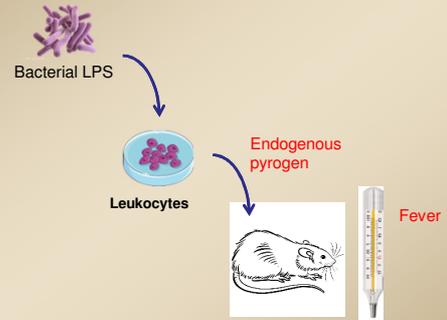
Despite extensive studies on the physiology of temperature regulation, the sequence of events leading to the elevation of body temperature in both clinical and experimental fevers is still unknown. It has been postulated that some product of tissue injury, liberated at sites of inflammation, may act upon the thermoregulatory centers to cause fever (1, 2). However, no such endogenous pyrogen has ever been identified in the circulation.

**JEM** Journal of Experimental Medicine

**THE DISCOVERY OF THE ENDOGENOUS PYROGENS**



**THE DISCOVERY OF THE ENDOGENOUS PYROGENS (1970s)**



**Leukocytic Pyrogen is the Same Molecule as Lymphocyte Activating Factor**

ADHERENT CELL FUNCTION IN MURINE T-LYMPHOCYTE ANTIGEN RECOGNITION  
 IV. Enhancement of Murine T-Cell Antigen Recognition by Human Leukocytic Pyrogen

By LANNY J. ROSENWASSER, CHARLES A. DINARELLO, AND ALAN S. ROSENTHAL

*From the Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20205*



1979 Sep 19;150(3):709-14

NATURE VOL. 312 20 JUNE 1985 ARTICLES 441

**Cloning, sequence and expression of two distinct human interleukin-1 complementary DNAs**

Carl J. March<sup>1</sup>, Bruce Mosley<sup>1</sup>, Alf Larsen<sup>1</sup>, Douglas Pat Cerretti<sup>1</sup>, Gary Braedt<sup>1</sup>, Virginia Price<sup>1</sup>, Steven Gillis, Christopher S. Henney, Shirley R. Kronheim<sup>1</sup>, Kenneth Grabstein<sup>1</sup>, Paul J. Conlon<sup>1</sup>, Thomas P. Hopp<sup>2</sup> & David Cosman<sup>1</sup>

Departments of <sup>1</sup> Protein Chemistry, <sup>2</sup> Molecular Biology and <sup>3</sup> Cellular Immunology, Immunex Corporation, 51 University Street, Seattle, Washington 98101, USA.

Two distinct but distantly related complementary DNAs encoding proteins sharing human interleukin-1 (IL-1) activity (termed IL-1α and IL-1β), were isolated from a macrophage cDNA library. The primary translation products of the genes are 271 and 269 amino acids long, although expression in Escherichia coli of the carboxy-terminal 159 and 153 amino acids produces IL-1 biological activity.

### CITOCINAS & FEBRE

**Table 1.** Proinflammatory cytokines that act as endogenous pyrogens.

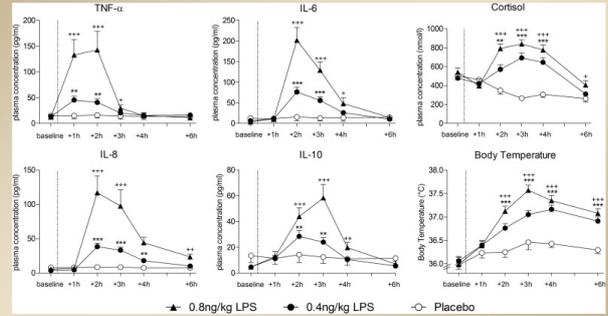
| Cytokine      | EP activity | Comment   | Reference     |
|---------------|-------------|---|---------------|
| IL-1          | +++         | The most potent EP in humans; both IL-1 $\alpha$ and IL-1 $\beta$ are EP  | [1, 22, 25]   |
| TNF- $\alpha$ | ++          | Possible role for both soluble and membrane-bound form  | [3, 77, 80]   |
| IL-6          | ++          | IL-6 acts distally of TNF and IL-1 in the cytokine cascade  | [39-41]       |
| IFN           | + / + +     | IFN- $\alpha$ is the most potent; IFN- $\beta$ less pyrogenic; IFN- $\gamma$ may be pyrogenic through induction of IL-1 and TNF | [1, 5, 43-45] |

NOTE. EP, endogenous pyrogen.

Netea et al. *Clin Infect Dis* 2000

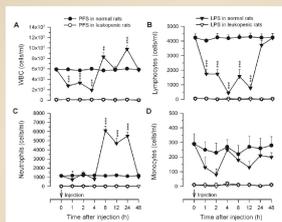
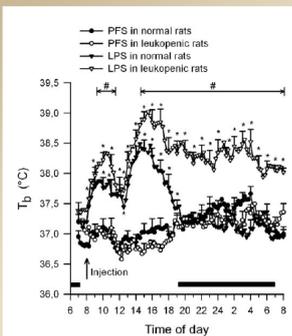
### A FEBRE TEM INÍCIO NA IMUNIDADE INATA

#### Humanos voluntários



Wegner et al. *Brain Behav Immun* 2014

### A FEBRE INDEPENDENTE DE LEUCÓCITOS CIRCULANTES



Leucopenia induzida por ciclofosfamida.

Tavares et al. *J Leukoc Biol* 2006

### A FEBRE INDEPENDENTE DE LEUCÓCITOS CIRCULANTES

**Table 1** Baseline characteristics

|   | Non-neutropenic sepsis (N=114,040) | Neutropenic sepsis (N=4027) |
|---|------------------------------------|-----------------------------|
| Male, %                                       | 54.9                               | 58.0                        |
| Mean age (SD), years                          | 63.6 (17.1)                        | 58.6 (15.5)                 |
| Lowest white cell count (SD), $\times 10^9/L$ | 12.8 (8.72)                        | 0.388 (0.33)                |
| Intubated, %                                  | 32.5                               | 30                          |
| Lowest MAP (SD), mmHg                         | 80.2 (26.2)                        | 68.5 (24.1)                 |
| Mean peak temperature (SD), °C                | 37.5 (0.96)                        | 38.1 (1.17)                 |

Weinkove et al. *Ann Hematol* 2015

**A FEBRE INDEPENDE DE LEUCÓCITOS CIRCULANTES**

**Disseminated *Mycobacterium* Infection in a Patient with Idiopathic CD4<sup>+</sup> T Lymphocytopenia Manifesting as Fever of Unknown Origin**

Jair Vargas,<sup>1</sup>  
Carmen Gamboa,<sup>1</sup> Domingo Negrin,<sup>1</sup>  
Maria Correa,<sup>1</sup> Cindy Sandoval,<sup>1</sup>  
Amerindia Aguiar,<sup>1</sup> Mercedes Prieto,<sup>1</sup>  
Alfonso J. Rodriguez-Morales,<sup>2</sup>  
Jacobus De Waard,<sup>2</sup> and Mitchell Yakrus<sup>3</sup>

<sup>1</sup>Collaborative Group of Clinical Infectious Diseases Research and <sup>2</sup>Tuberculosis Laboratory, Institute of Biomedicine, Caracas, and <sup>3</sup>Center for Research José Witremundo Torrealba, Universidad de Los Andes, Trujillo, Venezuela; and <sup>4</sup>Tuberculosis Laboratory Research, Tuberculosis/Mycobacterial Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

“Initial examination revealed fever (temperature, 39.0°C).”

**A FEBRE DEPENDE DE MACRÓFAGOS RESIDENTES**

**Fever and thermogenesis in response to bacterial endotoxin involve macrophage-dependent mechanisms in rats**

ROEL H. DERIJK, PAUL J. L. M. STRUIJBS, NICO VAN ROODEN, NANCY J. ROTHWELL, AND FRANK BERKENBOSCH  
Departments of Pharmacology and Histology, Free University, 1080 BT Amsterdam, The Netherlands, and Department of Physiological Sciences, University of Manchester, Manchester M13 9PT, United Kingdom.

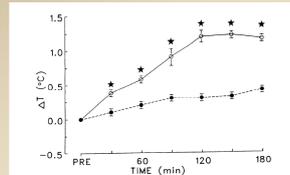


Fig. 2. Changes in colonic temperature in control (○) and in macrophage-depleted rats (●) obtained by repeated measurements over 3 h after intravenous administration of LPS (0.5 mg/kg). \**P* < 0.05 (independent *t* test); control vs. macrophage-depleted rats.

To deplete peripheral macrophages, rats were injected 4 days before the experiment with liposomes containing Cl<sub>2</sub>MDP (donated by Boehringer Mannheim; for preparation of the liposomes see Refs. 8, 36). Plasma IL-6 concentrations were measured 2 h after LPS administration, a time point that has previously been shown to represent the peak response of IL-6 (21).

*Am J Physiol* 1993

**PGE<sub>2</sub> na febre**



Anthony Milton

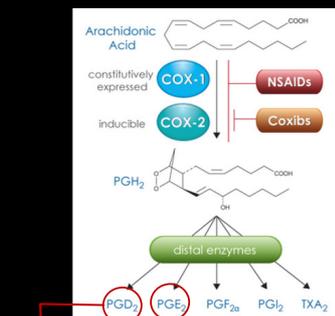
Descobriu que a PGE<sub>2</sub> é um potente agente indutor de febre.



John Vane

Descobriu que anti-inflamatórios não-esteroideais são inibidores da ciclooxigenase (COX), que por sua vez é essencial para a síntese de PGE<sub>2</sub>.

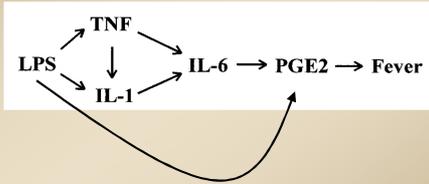
**COX na sickness syndrome**



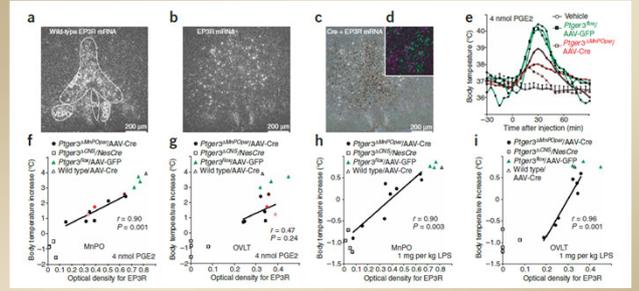
Sono  
Febre  
Anorexia  
Sono

Imagem de cayman.com

CITOCINAS, PGE<sub>2</sub> & FEBRE



Netea et al. *Clin Infect Dis* 2000



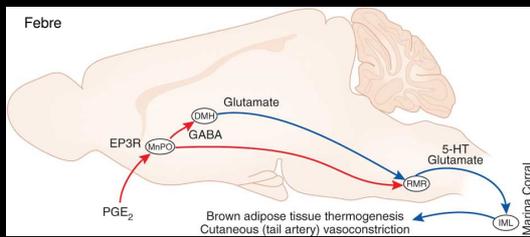
VOLUME 10 | NUMBER 9 | SEPTEMBER 2007 NATURE NEUROSCIENCE

REVIEW FOCUS ON NEURO-IMMUNE INTERACTIONS

nature neuroscience

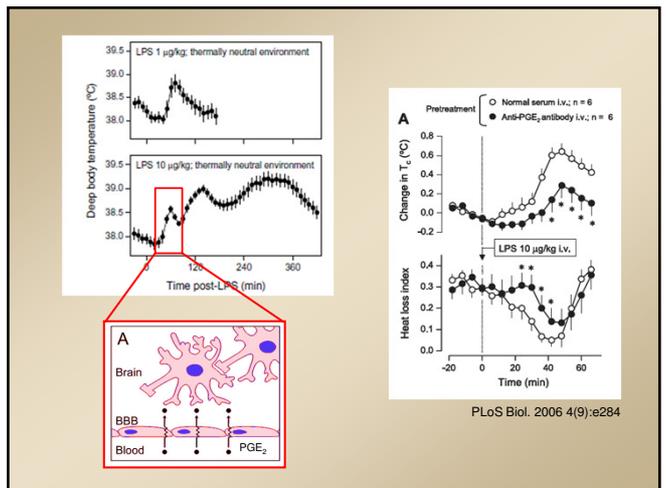
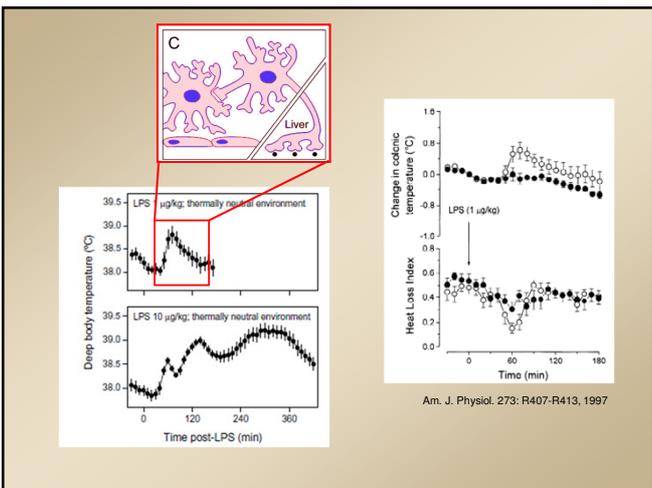
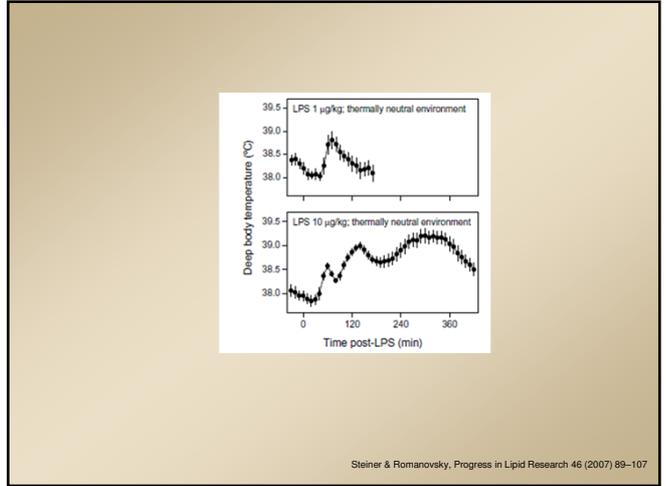
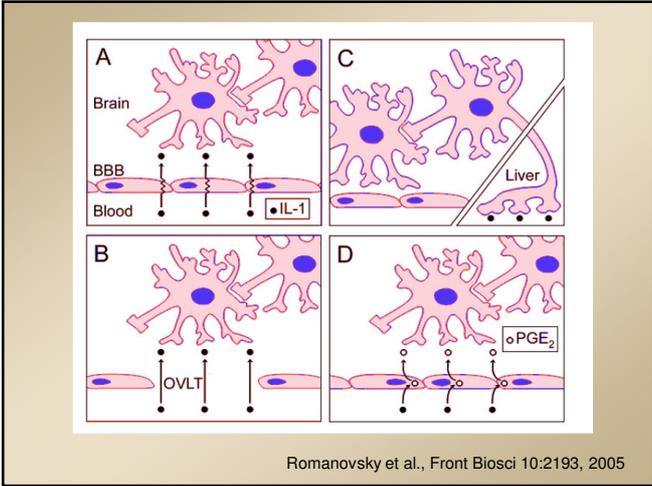
Neural circuitry engaged by prostaglandins during the sickness syndrome

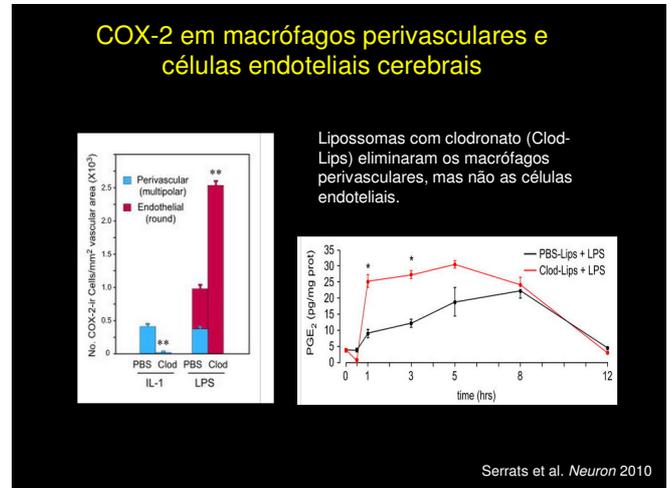
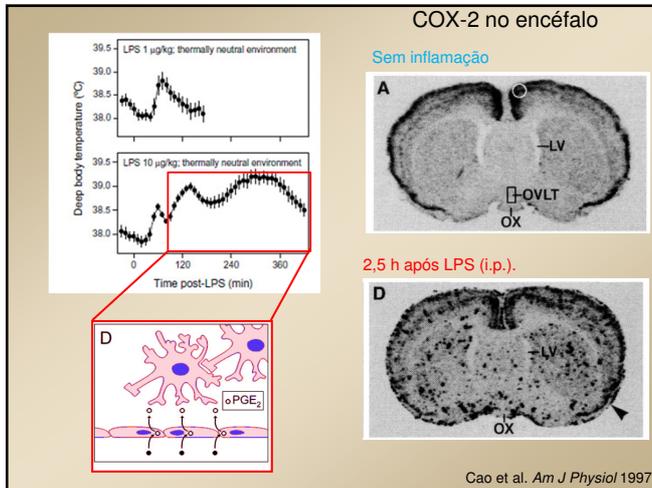
Clifford B Saper<sup>1</sup>, Andrej A Romanovsky<sup>2</sup> & Thomas E Scammell<sup>1</sup>



Mas como os sinais inflamatórios passam pela barreira hemato-encefálica?







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- ECTOTHERMIC SPECIES: Kluger et al. Fever and survival. *Science* 188: 166-8, 1975.
- FEVER-RANGE HYPERTHERMIA: Jiang et al. Febrile core temperature is essential for optimal host defense in bacterial peritonitis. *Infect Immun* 68: 1265-70, 2000.
- ANTIPYRETIC DRUGS: Husseini et al. Elevation of nasal viral levels by suppression of fever in ferrets infected with influenza viruses of differing virulence. *J Infect Dis* 145: 520-4, 1982.
- POIKILOTHERMY IN SEVERE INFECTION. Liu et al. Naturally occurring hypothermia is more advantageous than fever in severe forms of lipopolysaccharide- and *Escherichia coli*-induced systemic inflammation. *Am J Physiol Regul Integr Comp Physiol* 302: R1372-83, 2012.

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### ANIMAL RESEARCH



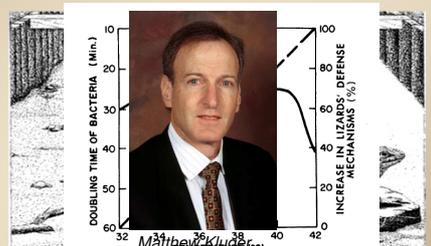
### PRIMEIRA EVIDÊNCIA DIRETA DO VALOR DA FEBRE

#### Fever and Survival

SCIENCE, VOL. 188  
4 November 1974; revised 8 January 1975

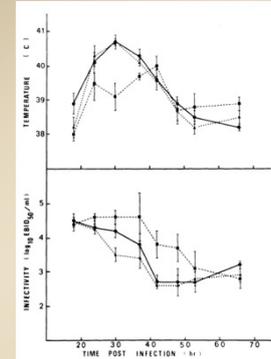
MATTHEW J. KLUGER  
*Department of Physiology, University of Michigan Medical School, Ann Arbor 48104*

DANIEL H. RINGLER  
MIRIAM R. ANVER  
*Unit for Laboratory Animal Medicine, University of Michigan Medical School*



The graph shows two data series plotted against temperature (°C) on the x-axis (ranging from 32 to 42). The left y-axis represents 'DOUBLING TIME OF BACTERIA (min.)' (ranging from 10 to 60), and the right y-axis represents 'INCREASE IN LIZARDS' DEFENSE MECHANISMS (%)' (ranging from 0 to 100). The bacterial doubling time (top line) increases as temperature rises, while the lizard defense mechanism increase (bottom line) decreases as temperature rises.

### VALOR DA FEBRE EM FERRETS

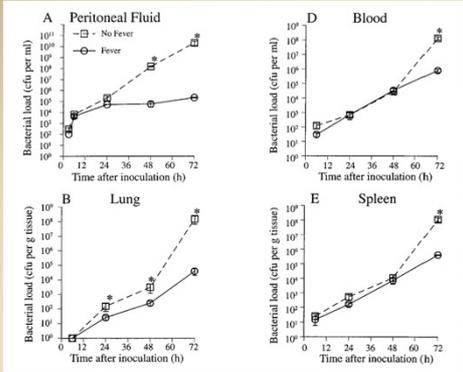


The graph has two y-axes and one x-axis. The x-axis is 'TIME POST INFECTION (hr)' from 20 to 70. The top y-axis is 'TEMPERATURE (°C)' from 38 to 41. The bottom y-axis is 'INFECTIVITY (log<sub>10</sub> ID<sub>50</sub>/ml)' from 2 to 5. Two lines with error bars are shown: one for temperature (top) and one for infectivity (bottom). Both lines show a peak around 30-40 hours post-infection.

**Figure 1.** Effect of shaving on mean increases in rectal temperature (top) and mean viral titers in nasal washes

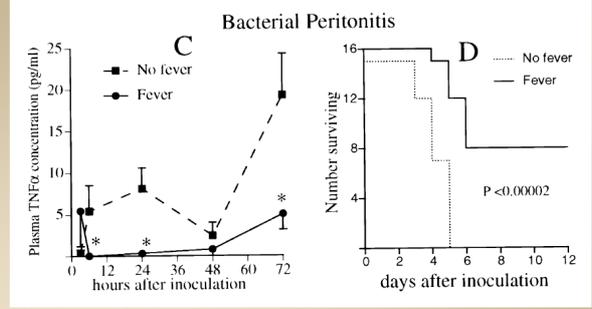
*J Infect Dis* 145: 520-4, 1982

**VALOR DA FEBRE EM CAMUNDONGOS**



Jiang et al., *Infection and Immunity* 68:1265, 2000

**VALOR DA FEBRE EM CAMUNDONGOS**

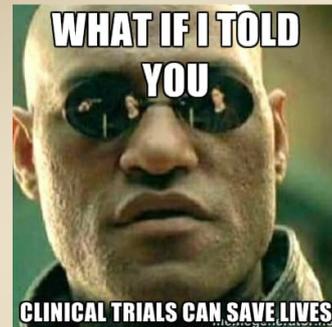


Jiang et al., *Infection and Immunity* 68:1265, 2000

**CLINICAL RESEARCH**



**CLINICAL RESEARCH**



**VALOR DA FEBRE EM HUMANOS**

**Adverse Effects of Aspirin, Acetaminophen, and Ibuprofen on Immune Function, Viral Shedding, and Clinical Status in Rhinovirus-Infected Volunteers**

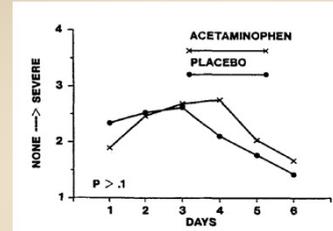
Neil M. H. Graham, Christopher J. Burrell, Robert M. Douglas,\* Pamela DeBelle, and Lorraine Davies

The Journal of Infectious Diseases 1996;162:1277-1282  
© 1996 by The University of Chicago. All rights reserved.  
0022-1899/96/6206-0008\$01.00

- Estudo sobre antipiréticos em voluntários infectados com rinovírus.
- Em relação aos pacientes que receberam placebo, pacientes tratados com aspirina ou paracetamol apresentaram:
  - ✓ Títulos mais baixos de anticorpos antivirais.
  - ✓ Tendência de maior proliferação viral.
  - ✓ Piores sintomas nasais.

**Acetaminophen: More harm than good for chickenpox?**

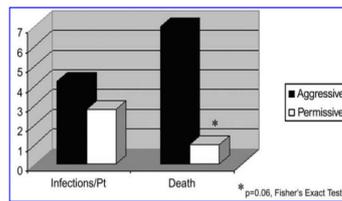
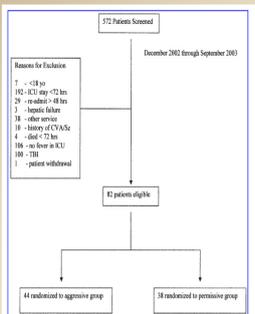
Timothy F. Doran, MD, Catherine De Angelis, MD, Rosemary A. Baumgardner, BA, and E. David Mellits, ScD  
From the Department of Pediatrics and the Department of Biostatistics and Pediatrics, The Johns Hopkins Medical Institutions, Baltimore



J Pediatr. 114: 1045-8, 1989

SURGICAL INFECTIONS  
Volume 6, Number 4, 2005  
© Mary Ann Liebert, Inc.  
DOI: 10.1093/sur.2005.6.369

**The Effect of Antipyretic Therapy upon Outcomes in Critically Ill Patients: A Randomized, Prospective Study**



**Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials**

Roman Prymula, Claire Anne Siegfried, Roman Chládek, Helena Zemčiková, Marie Vodvářka, Jan Smetana, Patricia Lomová, Eva Kádárová, David Bojars, Ludek Schuerman

| Serotype     | Prophylactic paracetamol |  | No prophylactic paracetamol |  |
|--------------|--------------------------|--|-----------------------------|--|
|              | N                        | Children with concentration $\geq 2$ $\mu\text{g/ml}$ , n (%) 95% CI | N                           | Children with concentration $\geq 2$ $\mu\text{g/ml}$ , n (%) 95% CI |
| Serotype 1   | 207                      | 202 (97.6%; 94.5-99.2)   | 226                         | 224 (99.1%; 96.8-99.9)   |
| Serotype 4   | 206                      | 205 (99.5%; 97.3-100)  | 226                         | 225 (99.6%; 97.6-100)  |
| Serotype 5   | 207                      | 206 (99.5%; 97.3-100)  | 227                         | 226 (99.6%; 97.6-100)  |
| Serotype 6B  | 206                      | 128 (62.1%; 55.1-68.8)   | 225                         | 170 (75.6%; 69.4-81.0)*  |
| Serotype 7F  | 208                      | 206 (99.0%; 96.6-99.9)   | 227                         | 226 (99.6%; 97.6-100)  |
| Serotype 9F  | 204                      | 200 (98.0%; 95.1-99.5)   | 225                         | 222 (98.7%; 96.2-99.7)   |
| Serotype 14  | 207                      | 206 (99.5%; 97.3-100)  | 225                         | 224 (99.6%; 97.5-100)  |
| Serotype 18C | 208                      | 199 (95.7%; 91.9-98.0)   | 227                         | 226 (99.6%; 97.5-100)  |
| Serotype 19F | 208                      | 203 (97.6%; 94.5-99.2)   | 227                         | 227 (100%; 98.4-100)   |
| Serotype 23F | 204                      | 164 (80.4%; 74.3-85.6)   | 225                         | 196 (87.1%; 82.0-91.2)   |

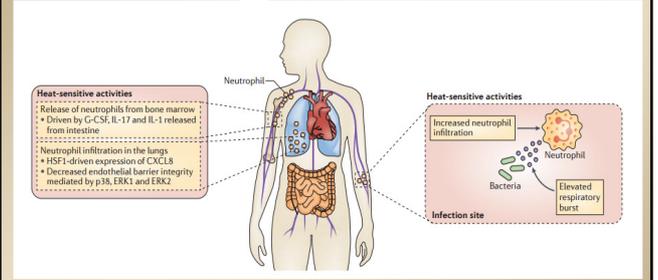
N=number of children with available results. GMC=geometric mean antibody concentration. PH1D-CV=tet-valent pneumococcal non-typeable Haemophilus influenzae protein D-conjugate vaccine. DTPa-HBV-IPV/Hb=hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H influenzae type B vaccine. ATP=according to protocol. \*Significant difference (no overlap of 95% CIs) between the prophylactic paracetamol group and the no prophylactic paracetamol group.

Table 1. Antipneumococcal IgG antibody responses 1 month after primary vaccination with PH1D-CV, DTPa-HBV-IPV/Hb, and human rotavirus vaccine with or without prophylactic administration of paracetamol (ATP immunogenicity cohort)

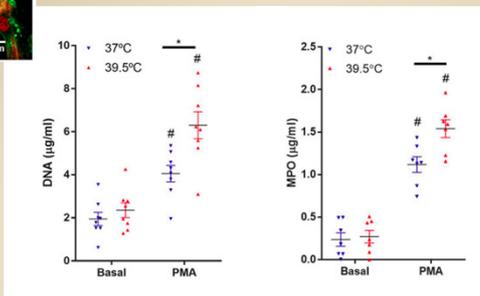
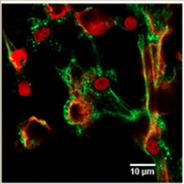
## MECHANISMS



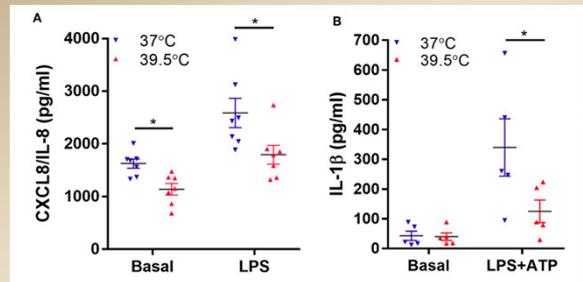
## Febre & imunidade inata

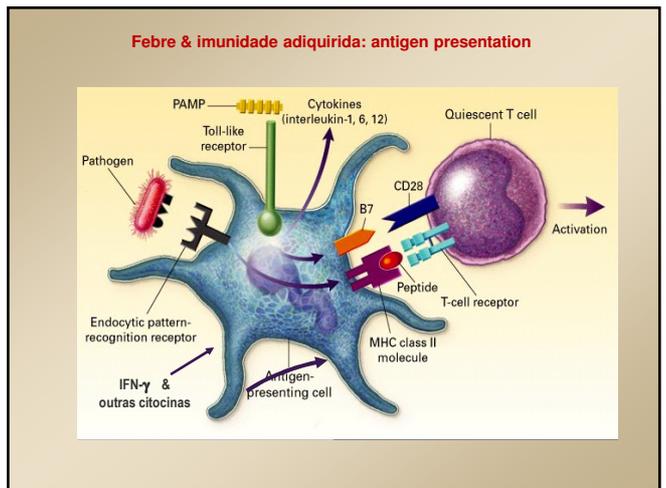
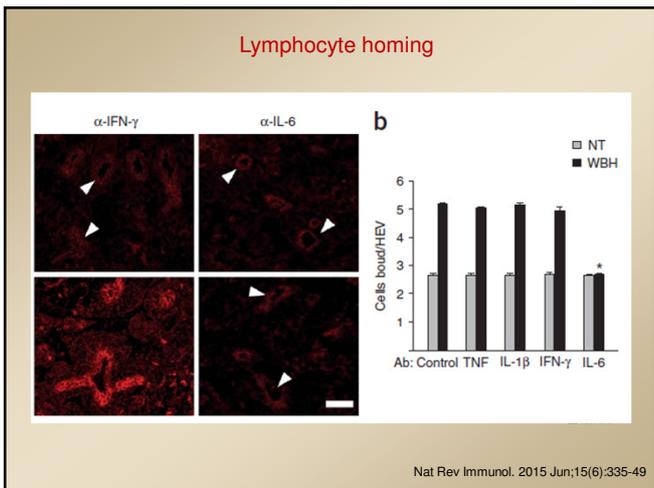
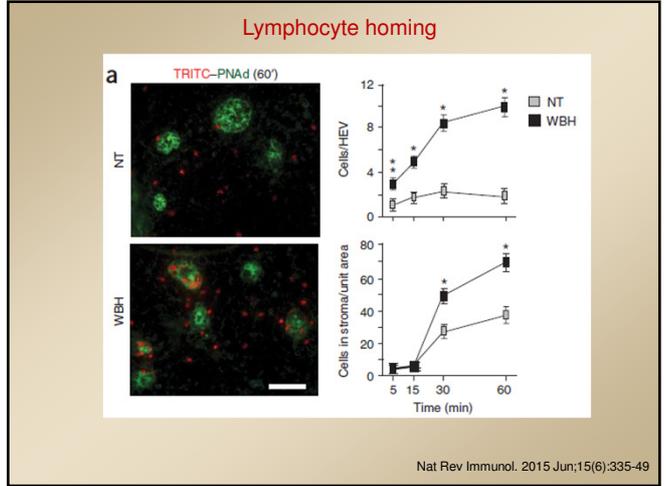
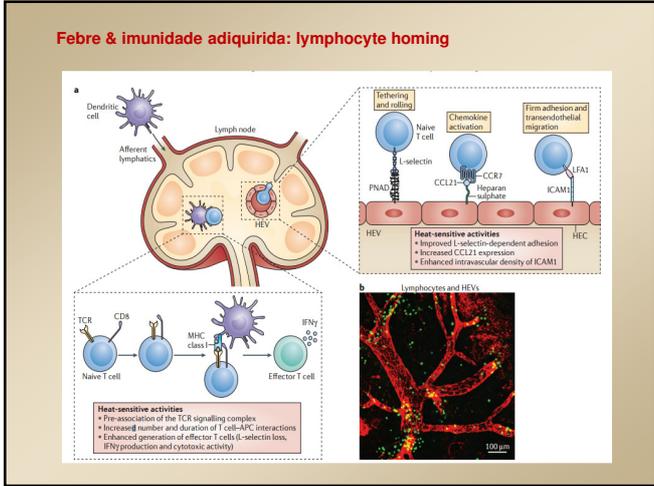


## NETosis

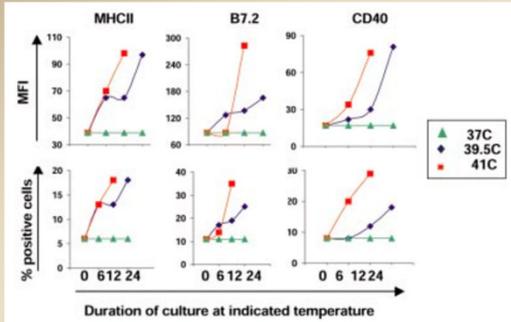


## Chemokine & Cytokine



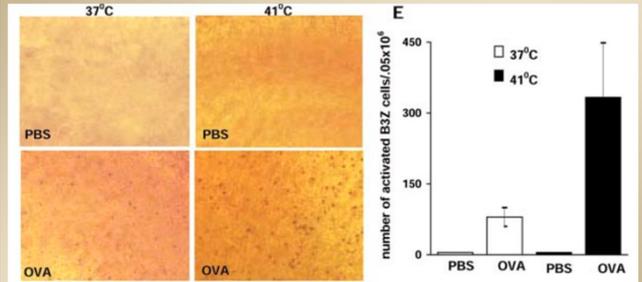


DC maturation



Int Immunol. 2003 Sep;15(9):1053-61

T cell proliferation



Int Immunol. 2003 Sep;15(9):1053-61

ENTÃO POR QUE A FEBRE-FOBIA?



Em hospital nos EUA (Baltimore, MD)

- A visão de que a febre é a própria doença e deve ser eliminada a qualquer custo persiste.
- 56% dos entrevistados têm grande preocupação com os efeitos prejudiciais da febre.
- 25% administram antipiréticos para febres inferiores a 38,0°C.
- Maior preocupação é com lesão cerebral e convulsões.

Crocetti et al., *Pediatrics* 107:1241, 2007

FEBRE E CONVULSÕES: FATO OU MITO?

ARTICLE IN PRESS  
EUROPEAN JOURNAL OF PEDIATRIC NEUROLOGY XXX (2013) 1-6  
**Do antipyretics prevent the recurrence of febrile seizures in children? A systematic review of randomized controlled trials and meta-analysis**  
Ehud Rosenbloom<sup>a,c,h</sup>, Yaron Finkelstein<sup>b,c,c,h</sup>, Thomasin Adams-Webber<sup>d</sup>, Eran Kozier<sup>f,g</sup>

| Study or Subgroup   | antipyretics |       | Placebo |       | Weight | Odds Ratio<br>M-H, Random, 95% CI | Odds Ratio<br>M-H, Random, 95% CI |
|---|--------------|-------|---------|-------|--------|-----------------------------------|-----------------------------------|
|   | Events       | Total | Events  | Total |        |                                   |                                   |
| Strengell et al   | 46           | 197   | 8       | 34    | 28.7%  | 0.99 [0.42, 2.34]                 |                                   |
| Uhari et al   | 2            | 40    | 3       | 39    | 6.2%   | 0.63 [0.16, 4.00]                 |                                   |
| Van Stuijvenberg et al  | 31           | 111   | 36      | 119   | 65.1%  | 0.89 [0.51, 1.58]                 |                                   |
| Total (95% CrI)   |              | 348   |         | 192   | 100.0% | 0.90 [0.57, 1.43]                 |                                   |
| Total events  |              |       |         |       |        | 79                                | 47                                |
| Heterogeneity: Tau <sup>2</sup> = 0.00, Chi <sup>2</sup> = 0.19, df = 2 (P = 0.91), I <sup>2</sup> = 0% |              |       |         |       |        |                                   |                                   |
| Test for overall effect: Z = 0.45 (P = 0.64)  |              |       |         |       |        |                                   |                                   |

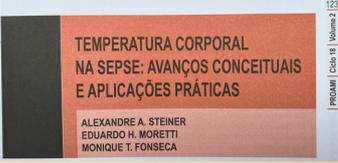
Antipiréticos não reduzem a recorrência de convulsões associadas a infecções em crianças.

Não há evidência de danos neurológicos em associação com a febre de até 42°C.

Podium: the big idea

**Should we let fever run its course in the early stages of COVID-19?**

Alexandre A Steiner  
Departamento de Imunologia, Instituto de Ciencias Biomedicas, Universidade de



Journal of the Royal Society of Medicine 2020, 113(10): 481-486  
DOI: 10.1177/0962280220951544

123 | PROAMT | CUBAS | Volume 2

“Com base nas evidências experimentais e clínicas, é lógico recomendar que medicamentos antipiréticos sejam evitados nos primeiros dias de uma infecção.”

“Uma estratégia mais permissiva com relação à febre pode reduzir as chances de infecções mais prolongadas e, conseqüentemente, de complicações.”

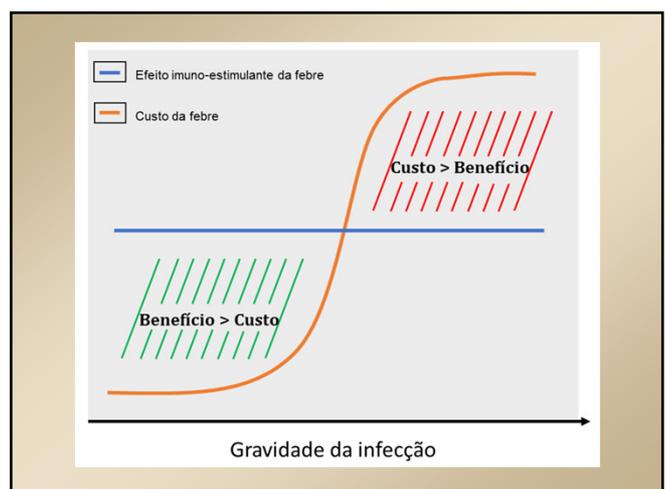
### ROADMAP



- 1) Historical highlights
- 2) Mechanisms of fever induction
- 3) Impacts of fever on host defense: approaches
- 4) Impacts of fever on host defense: mechanisms & therapy
- 5) Hypothermia as an alternative host defense strategy

### CUSTO-BENEFÍCIO DA FEBRE

| Benefícios                                       | Custos                              |
|--|-------------------------------------|
| ↑ Fagocitose                                     | ↑ Consumo de substratos energéticos |
| ↑ Migração leucocitária                          | ↑ Consumo de oxigênio               |
| ↑ Apresentação de antígenos                      | ↑ Perda de água                     |
| ↑ Proliferação linfocitária                      | ↑ Edema pulmonar                    |
| ↑ Produção de anticorpos                         | ↑ Endotoxemia                       |
| Tira muitos microorganismos da temperatura ótima | ↑ Estresse oxidativo                |



AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 185 2012

### Fever Control Using External Cooling in Septic Shock A Randomized Controlled Trial

Frédérique Schortgen<sup>1,2</sup>, Karine Clabault<sup>3</sup>, Sandrine Katsahian<sup>4</sup>, Jerome Devaquet<sup>5</sup>, Alain Mercat<sup>6</sup>, Nicolas Deye<sup>7</sup>, Jean Dellamonica<sup>8</sup>, Lila Bouadma<sup>9</sup>, Fabrice Cook<sup>10</sup>, Olfa Beji<sup>1</sup>, Christian Brun-Buisson<sup>1</sup>, François Lemaire<sup>1</sup>, and Laurent Brochard<sup>1,2,11</sup>

**AT A GLANCE COMMENTARY**

**Scientific Knowledge on the Subject**  
The benefits and risks of fever control in severe sepsis remain debated. Although fever is common in sepsis, few comparative studies on fever management are available.

**What This Study Adds to the Field**  
Fever control using external cooling in sedated patients with septic shock is safe and decreases vasopressor requirement and early mortality.

### Hypothermia in sepsis

| Reference                        | Mortality rate |                | APACHE II ou SOFA |                |
|----------------------------------|----------------|----------------|-------------------|----------------|
|                                  | Hypothermia    | No hypothermia | Hypothermia       | No hypothermia |
| Intensive Care Med 30: 811, 2004 | 80%            | 48%            | 10.2              | 7.2            |
| Crit Care 17: R271, 2013         | 52%            | 25%            | 28                | 22             |
| Crit Care Med 43: 1165, 2015     | 50%            | 25%            | 21                | 16             |

*J Appl Physiol* 120: 1394–1401, 2016.  
First published March 17, 2016; doi:10.1152/jappphysiol.00004.2016.

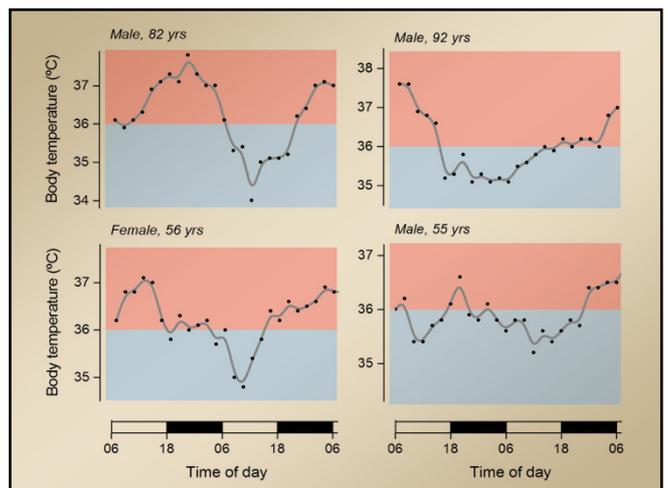
### Spontaneous hypothermia in human sepsis is a transient, self-limiting, and nonterminal response

Monique T. Fonseca,<sup>1</sup> Abner C. Rodrigues,<sup>2</sup> Luana C. Cezar,<sup>1</sup> Andre Fujita,<sup>2</sup> Francisco G. Soriano,<sup>3</sup> and Alexandre A. Steiner<sup>1</sup>

<sup>1</sup>Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil; <sup>2</sup>Institute of Mathematics and Statistics, University of São Paulo, São Paulo, Brazil; <sup>3</sup>Medical School, University of São Paulo, São Paulo, Brazil

**NEW & NOTEWORTHY**

*Hypothermia in sepsis is often fought off with active rewarming. In this study, we had access to a rare cohort of septic patients in which hypothermia was allowed to run its natural course. The study revealed that, contrary to conventional wisdom, hypothermia in human sepsis is usually transient, self-limiting, and nonterminal. This clinical finding parallels animal studies indicating that, like fever, regulated hypothermia is an inherent component of the systemic inflammatory response to infection.*



### What have we learned from animal models?

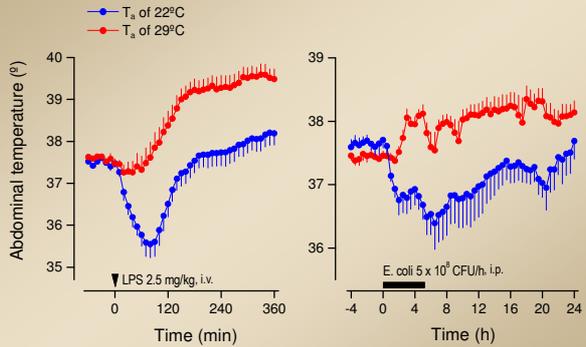
In rats with endotoxic or septic shock:

*Looks like a regulated response!*



- The **hypothermia** prevails over **fever** when systemic inflammation is more severe.
- The **hypothermia** begins early (before organ failure), and is often self-limiting and transient.
- The **hypothermia** is NOT brought about by skin vasodilation.
- The **hypothermia** results from suppression of thermogenesis when thermogenic capacity is unimpaired.
- Rats seek **cooler** environments to develop **hypothermia** in severe systemic inflammation.

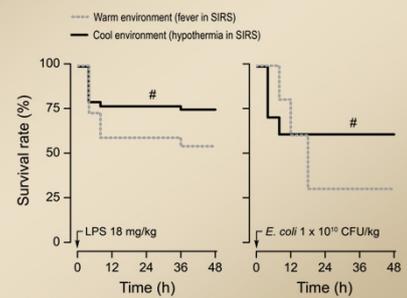
Inflamaç o sist mica grave

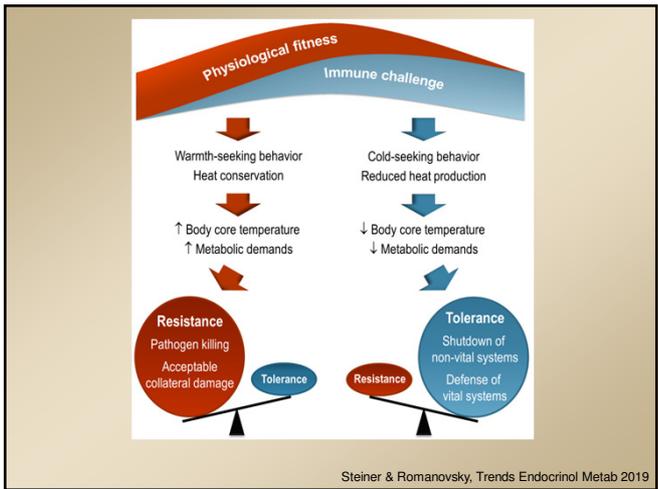
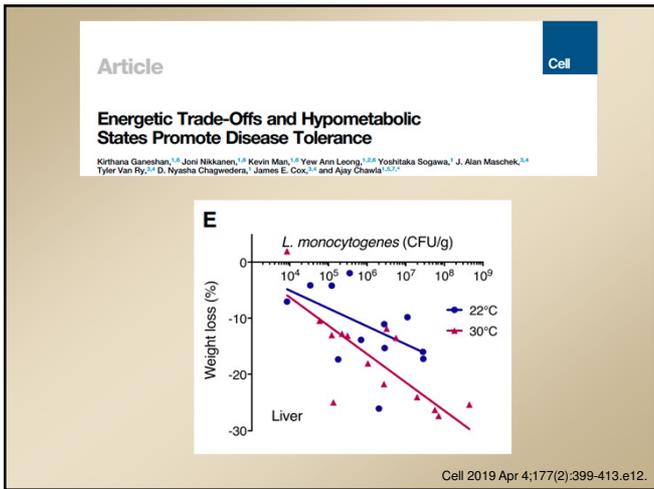
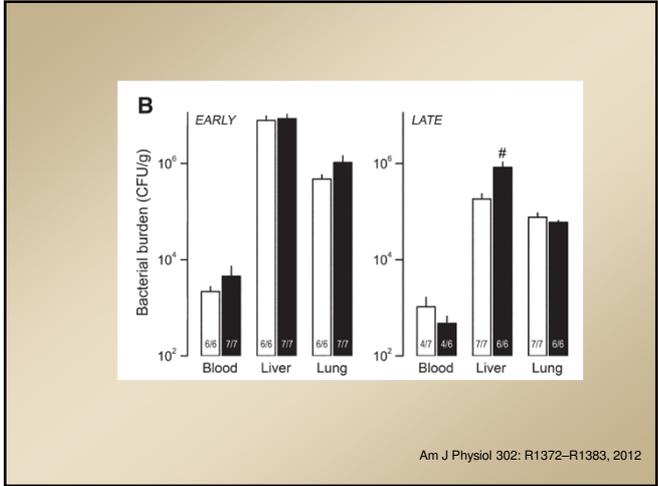
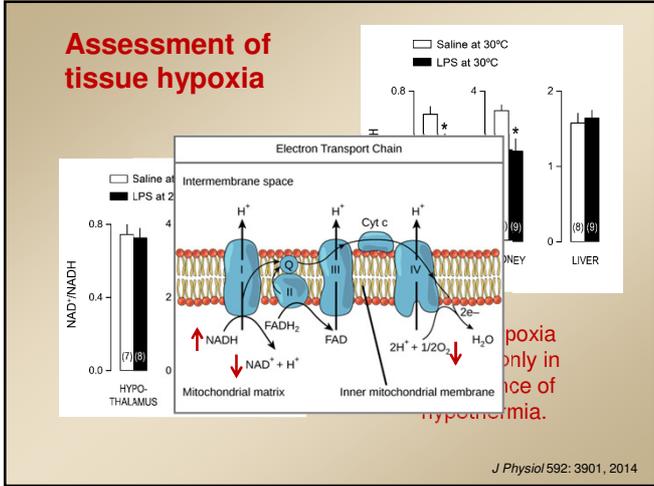


*Am J Physiol Regul Integr Comp Physiol* 302: R1372-R1383, 2012.  
First published April 18, 2012; doi:10.1152/ajpregu.00023.2012.

### Naturally occurring hypothermia is more advantageous than fever in severe forms of lipopolysaccharide- and *Escherichia coli*-induced systemic inflammation

Elaine Liu,<sup>1</sup> Kevin Lewis,<sup>1</sup> Hiba Al-Saffar,<sup>1</sup> Catherine M. Krall,<sup>1</sup> Anju Singh,<sup>2</sup> Vladimir A. Kulchitsky,<sup>3,4</sup> Joshua J. Corrigan,<sup>1</sup> Christopher T. Simons,<sup>5</sup> Scott R. Petersen,<sup>4</sup> Florin M. Munteanu,<sup>4</sup> Chandra S. Bakshi,<sup>2</sup> Andrej A. Romanovsky,<sup>3,4</sup> Timothy J. Sellati,<sup>2</sup> and Alexandre A. Steiner<sup>1</sup>







John Maynard Keynes (1883-1946)  
Economista

“A verdadeira dificuldade não está em aceitar ideias novas, mas em escapar das ideias antigas”.

"Discovery consists of seeing what everybody has seen and thinking what nobody has thought."



Albert Szant-Gyorgyi (1893-1966)  
Nobel Prize in Physiology or Medicine (1937)