Animal models of sepsis

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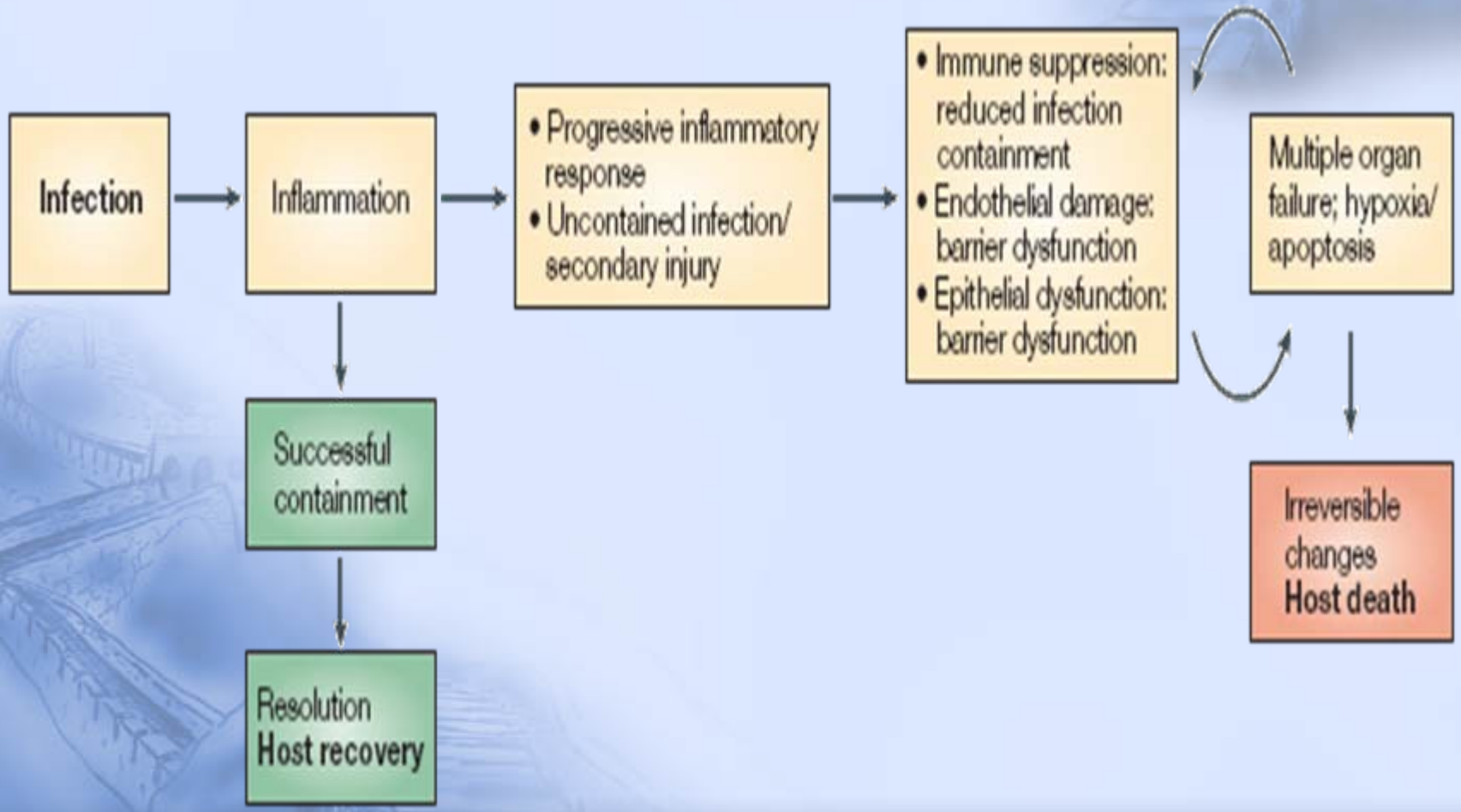
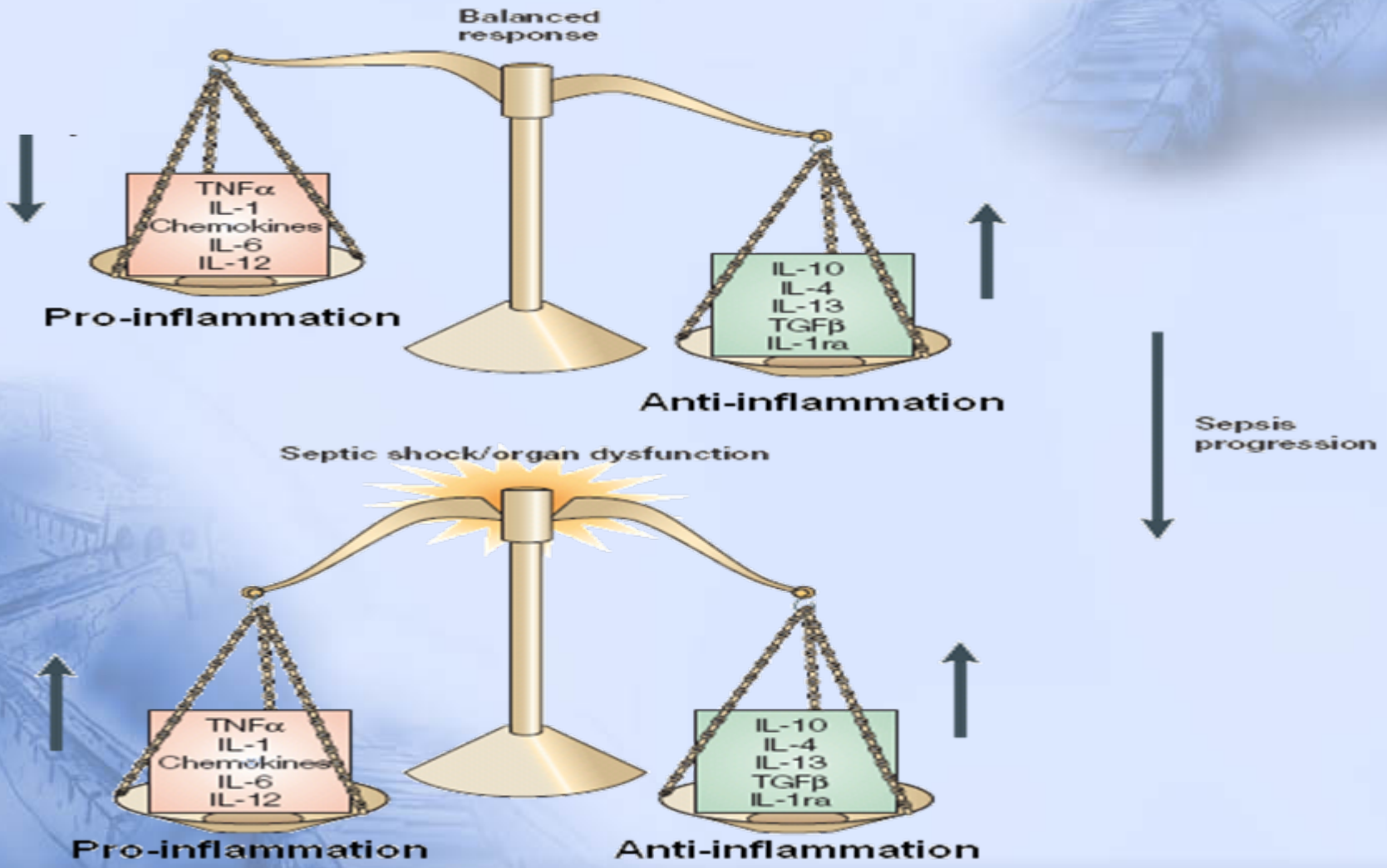
12/7/2010

Sepsis: systemic inflammatory response to infection



Marshall JC. Nat Rev Drug Discov. 2003; 2: 391-405.

Molecular pathogenesis



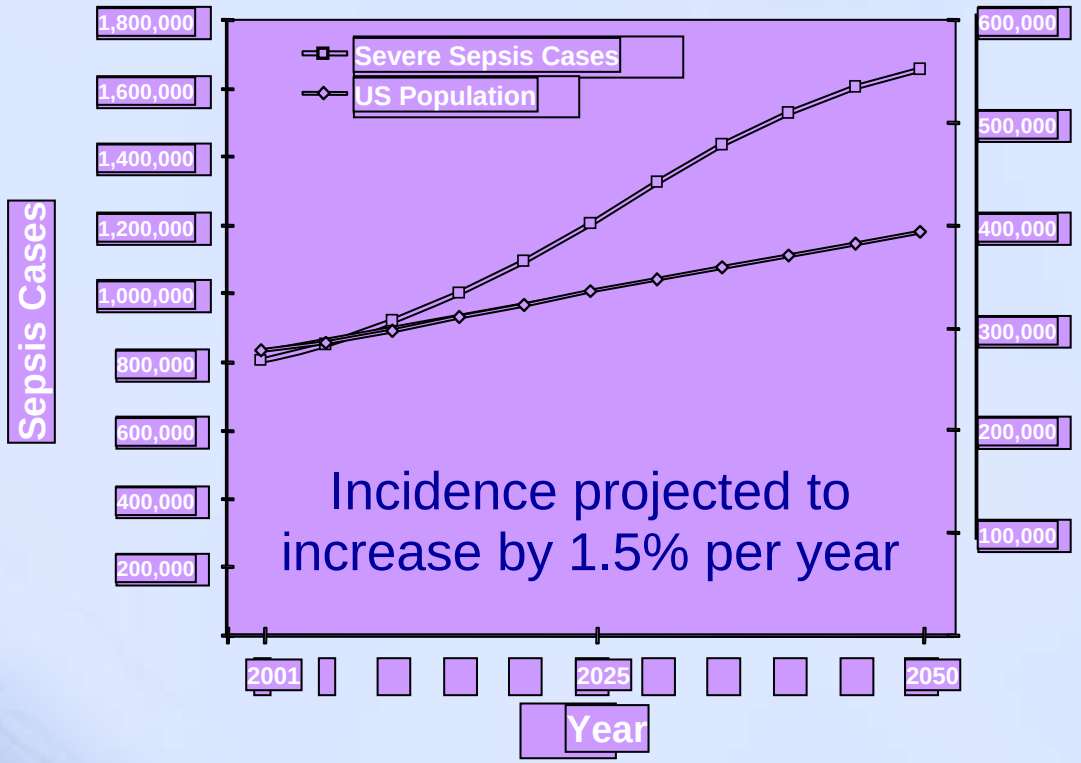
Marshall JC. Nat Rev Drug Discov. 2003; 2: 391-405.

Incidence of sepsis

Today

>750,000 cases of severe sepsis/year in the US

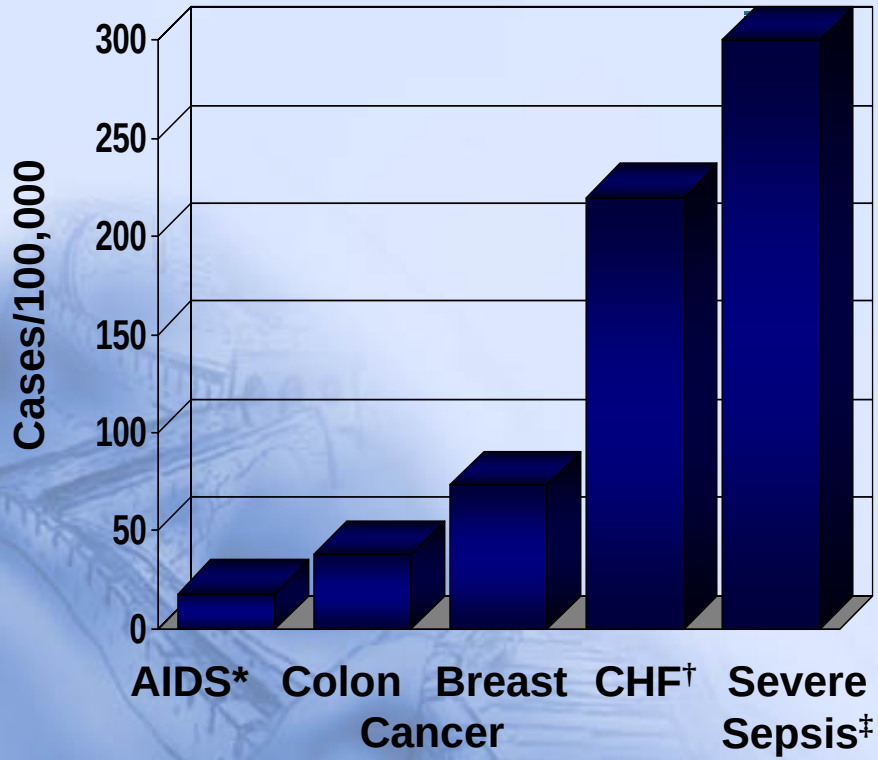
Future



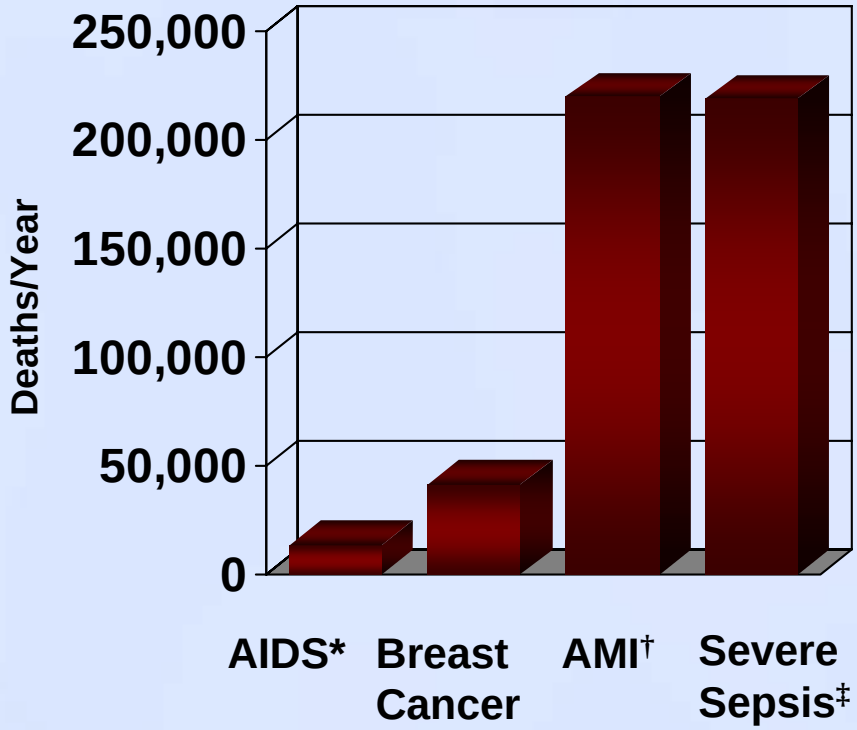
Crit Care Med. 2001;29(7):1303-1310.

Comparison with other major diseases

Incidence of Severe Sepsis

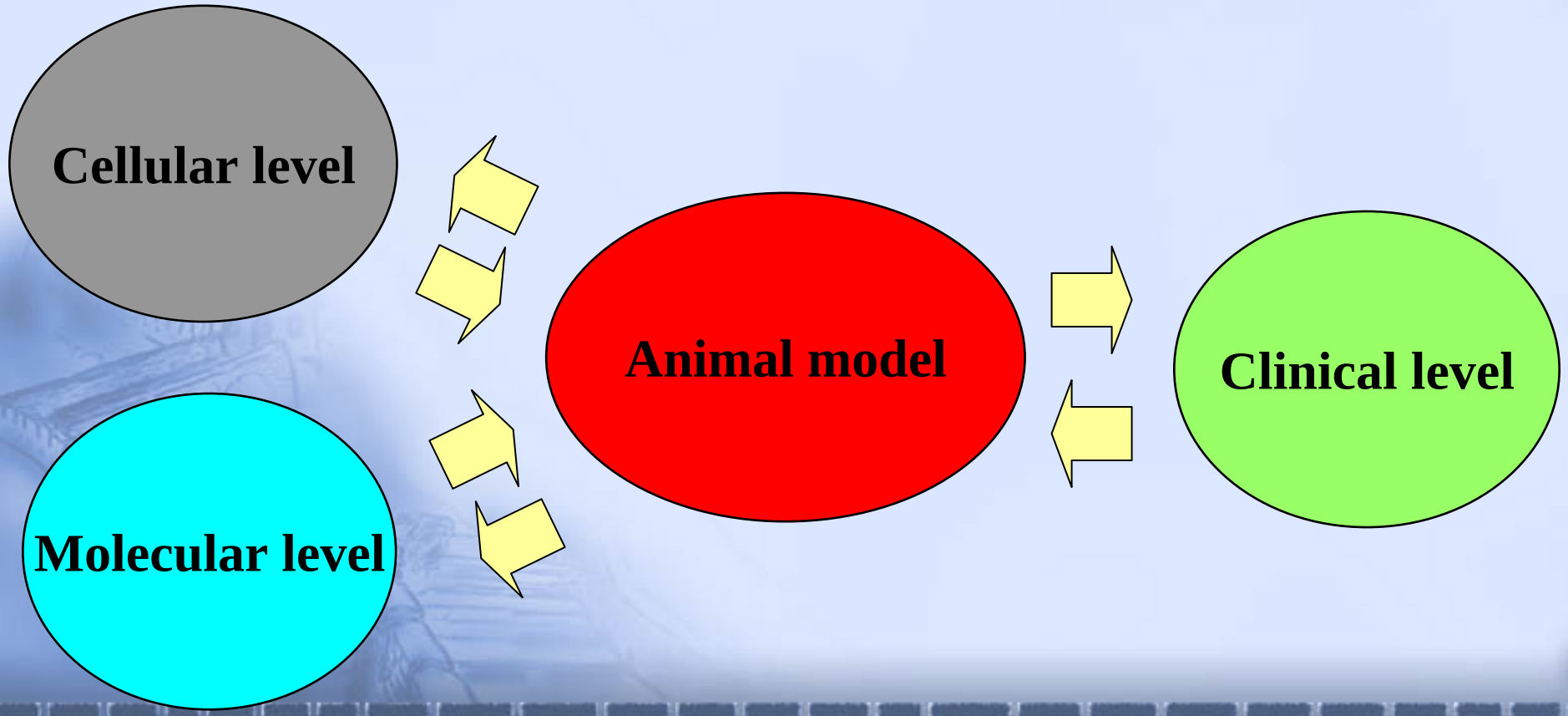


Mortality of Severe Sepsis



National Center for Health Statistics, 2001. American Cancer Society, 2001. American Heart Association. 2000. ‡Angus DC et al. *Crit Care Med.* 2001;29(7):1303-1310.

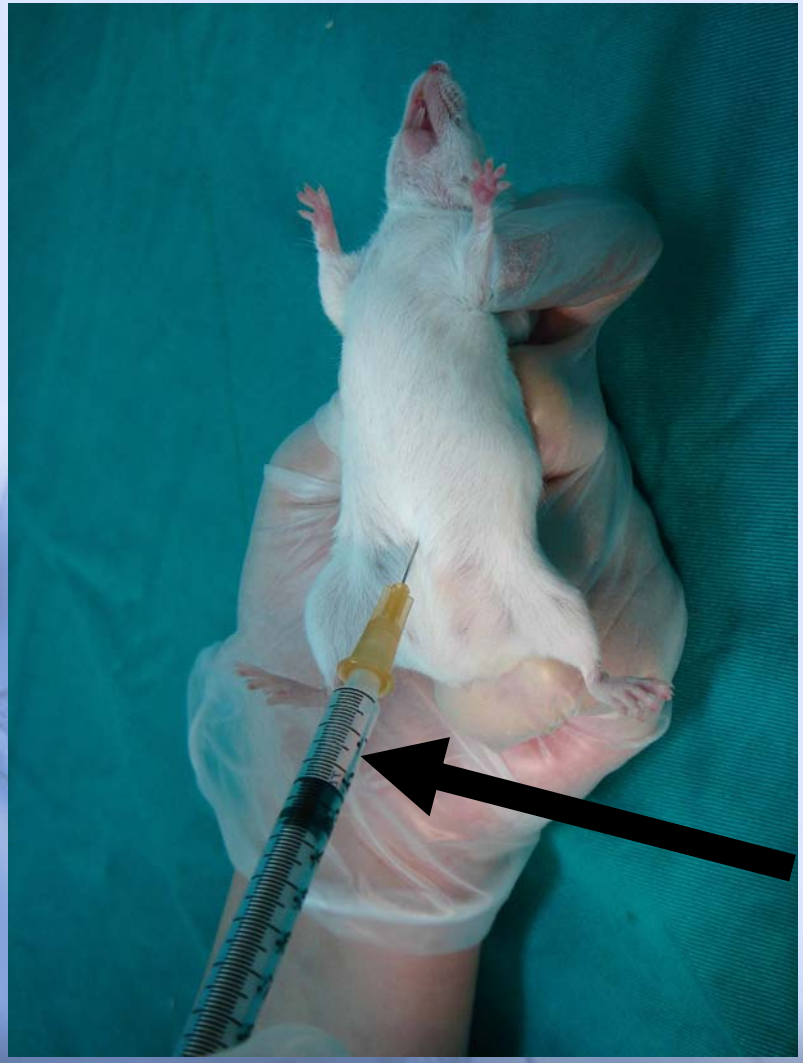
Central role of animal model in sepsis study, particularly for pre-clinical trials



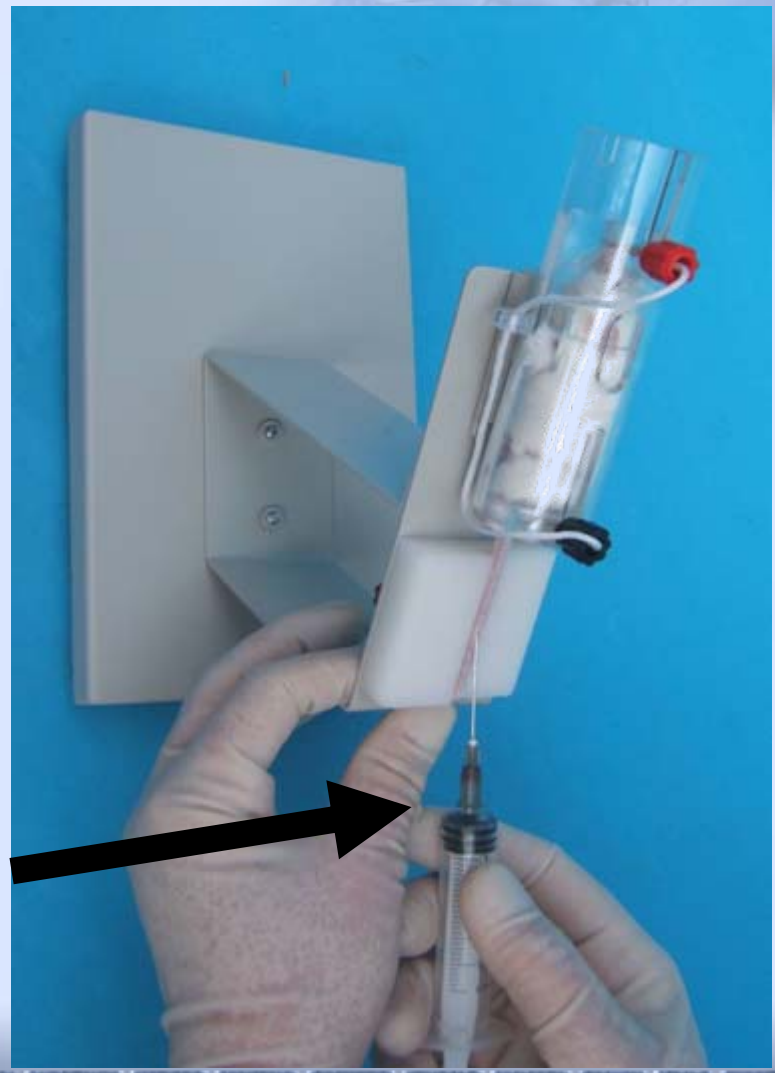
Types of sepsis models

- **Toxaemia models**
- **Bacterial infection models**
- **Host-barrier disruption models**

Toxaemia models: LPS model



LPS



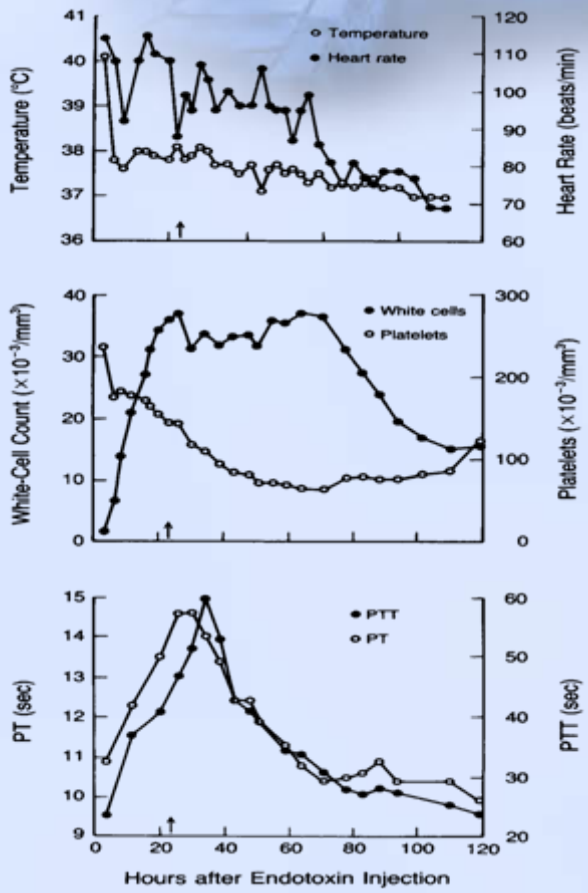
LPS induces sepsis in human

Table 1. Hemodynamic Measurements and Vasopressor Administration after the Injection of *S. minnesota* Endotoxin.*

Hours after Endotoxin Injection	Weight	Cumulative Fluid Intake in Excess of Output	Dopamine	Norepinephrine	Mean Arterial Pressure	Pulmonary-Capillary Wedge Pressure	Cardiac Index	Systemic-Vascular-Resistance Index	Stroke-Volume Index	Left Ventricular-Stroke-Work Index
	kg	ml	μg/kg/min	μg/min	mm Hg		liters/min/m²	dyn · sec · cm⁻⁵ · m²	ml/m²	g/min/m²
5	66.4	4,000	5.0	—	47	—	—	—	—	—
12	—	5,000	12.4	9.4	60	3.0	5.0	800	46	29.4
17	—	6,900	12.4	9.4	77	4.0	4.6	1165	43	35.0
24	—	9,200	8.8	15.6	86	10.0	3.5	1896	40	47.8
28	—	10,300	4.4	15.6	78	12.0	3.3	1781	31	39.6
32	—	10,600	1.6	15.6	82	16.0	3.8	1560	40	42.4
44	—	14,600	1.6	2.1	71	21.0	4.9	933	46	44.4
50	76.5	14,900	1.6	—	78	15.0	4.3	1338	45	50.1
72	75.2	15,775	—	—	84	12.0	3.0	2000	39	44.5
Normal range†	—	—	—	—	70–105	2.0–10.0	2.6–4.2	1200–2800	30–65	30–90

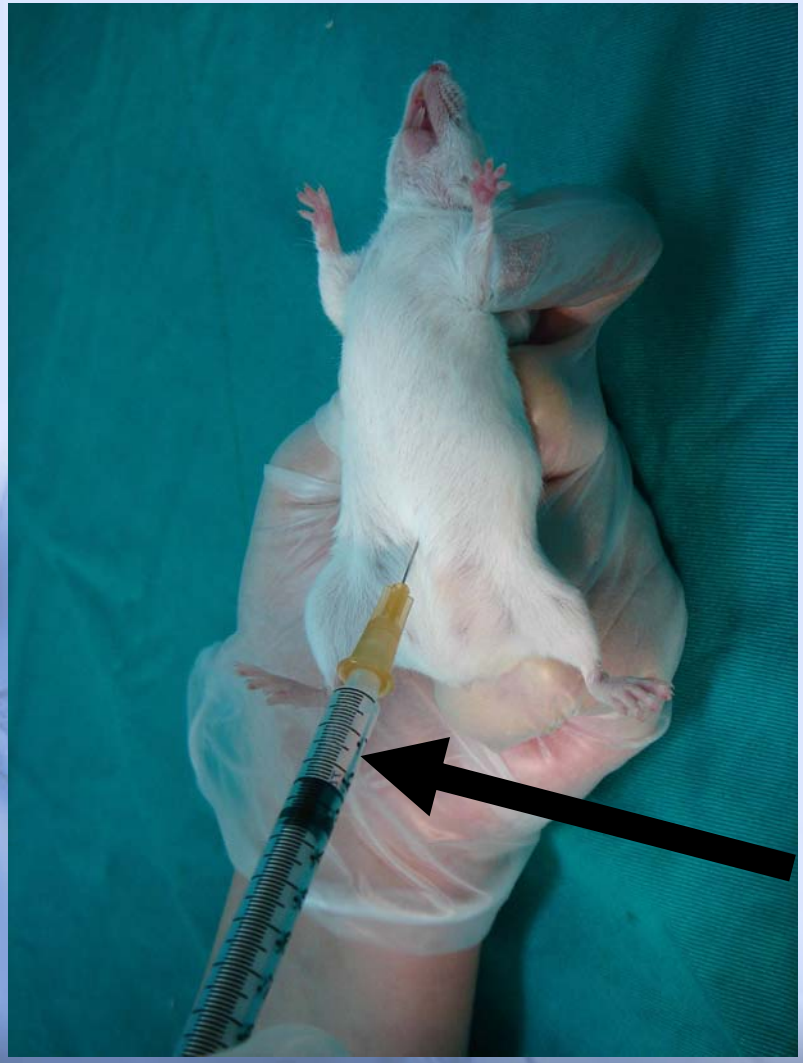
Table 2. Serial Serum Concentrations of Endotoxin and Cytokines after the Injection of *S. minnesota* Endotoxin.*

Hours after Endotoxin Injection	Endotoxin	TNF-α by ELISA	TNF-α by Bioassay	Interleukin-6	Interleukin-8	G-CSF
	EU/ml†	pg/ml				
3.6	NA	14,630	9,157	NA	NA	NA
6.8	0.38	147	17	263,510	16,410	NA
11.5	<0.05	NA	NA	51,910	3,190	NA
22.5	0.19‡	NA	NA	1,620	520	277,070
24.0	0.80‡	22	<10	927	380	230,690
24.5	<0.05	NA	NA	489	230	174,200
25.5	<0.05	16	<10	480	210	164,870
26.5	NA	<10	<10	590	650	10,630
48.0	NA	<10	<10	NA	NA	NA
Normal value§	<0.05	<10	<10	<100	<50	<100

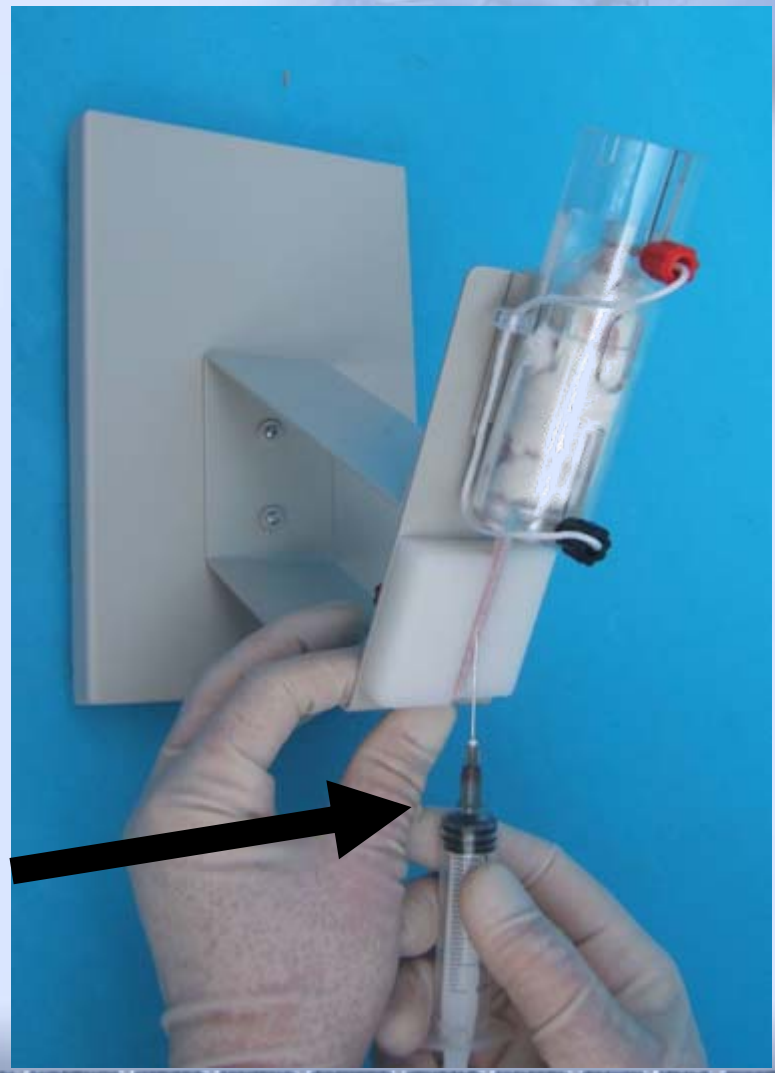


N Engl J Med. 1993. 20;328(20):1457-60.

Toxaemia models: LPS model

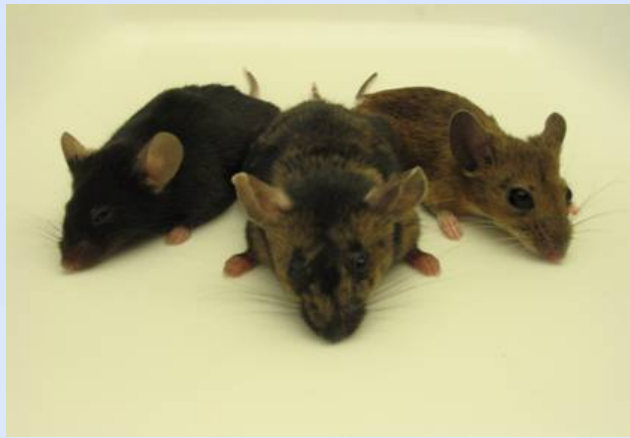


LPS



Variability factors of the model

- Type of toxin utilized (LPS subtype or use of sensitizing agent [d-Gal])
- Host species and strain
- Lethal or sub-lethal dose
- Route of administration



J. Clin. Invest. 2009; 119:2868–2878. Nat Rev Drug Discov. 2003; 2: 391-405.

Controversial results between LPS model and clinical trial of anti-IL-1 receptor

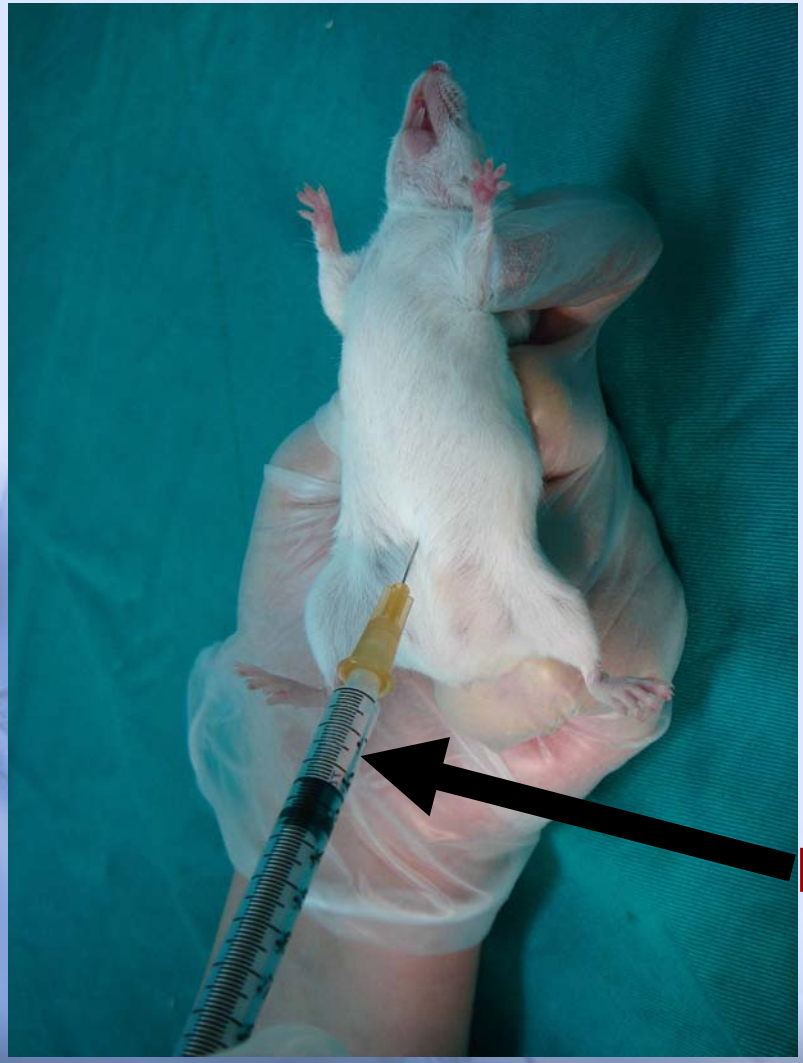
- **Mouse result:** an IL-1 receptor antibody has therapeutic efficacy against LPS induced sepsis

- **Human result:** There was not a statistically significant increase in survival time for anti-IL1 receptor treatment

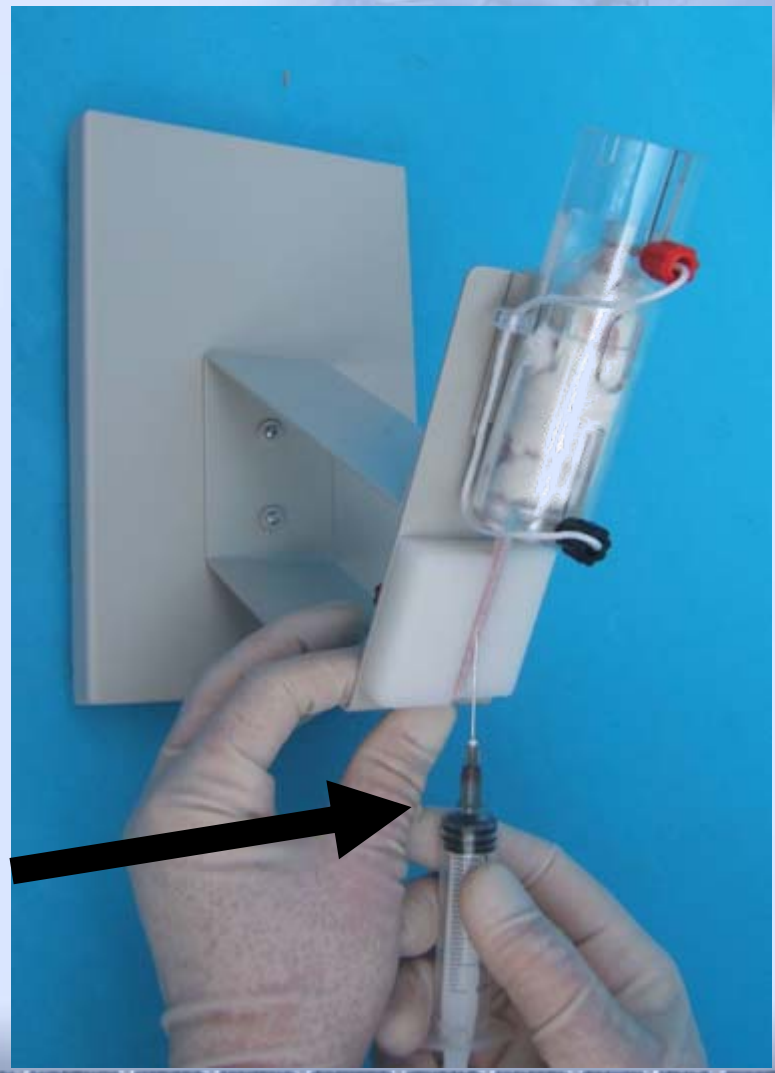
J Surg Res. 1993 Apr;54(4):316-21.

JAMA. 1994 Jun 15;271(23):1836-43.

Bacterial infection models



Bacteria



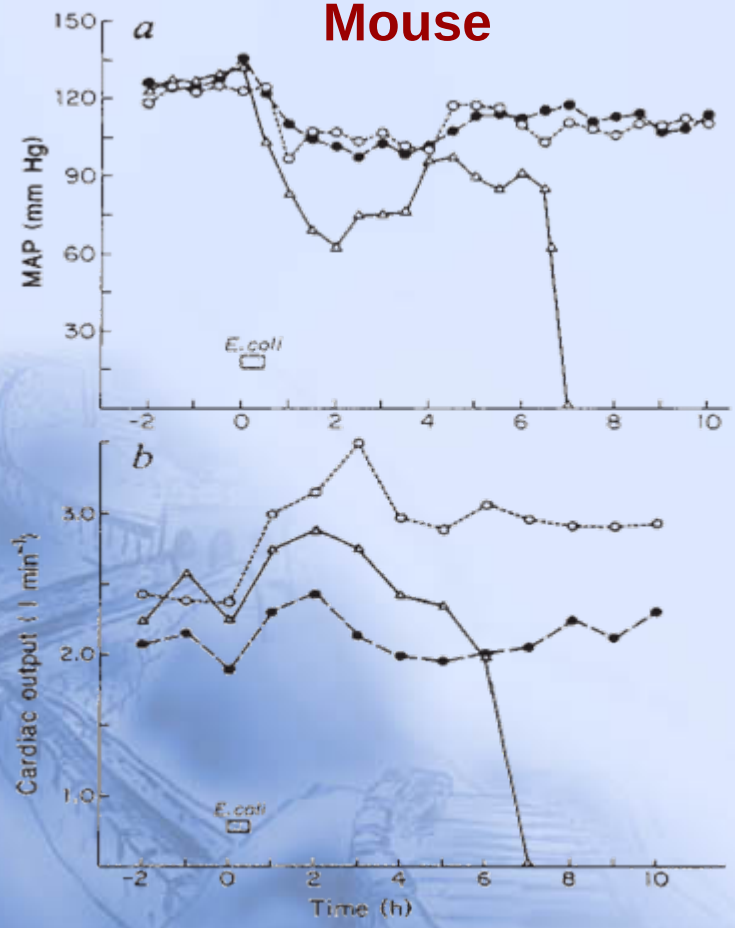
Variability factors of the model

- Bacterial load
- Bacterial strain
- Host strain
- Route of administration

J. Clin. Invest. 2009; 119:2868–2878. Nat Rev Drug Discov. 2003; 2: 391-405.

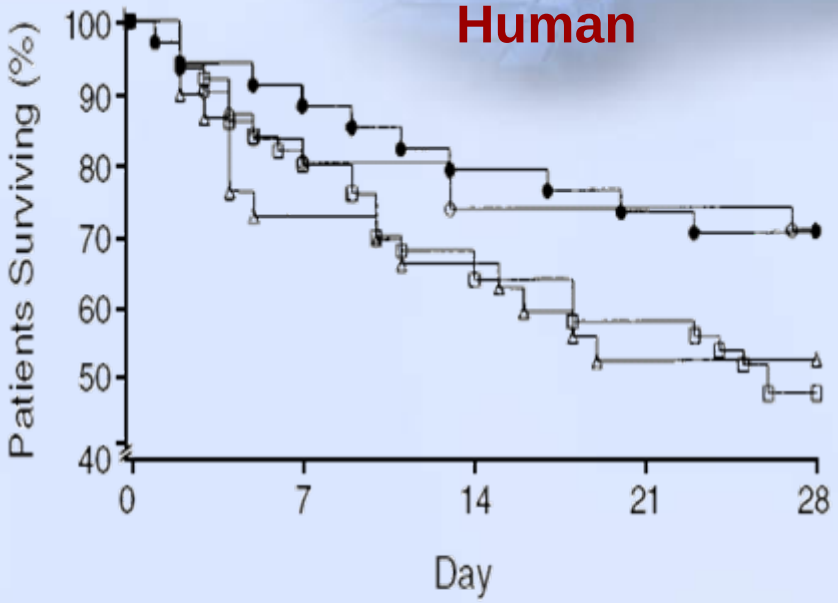
Controversial results between this model and clinical trial of anti-TNF-a receptor

Mouse



Nature. 1987 Dec 17-23;330(6149):662-4.

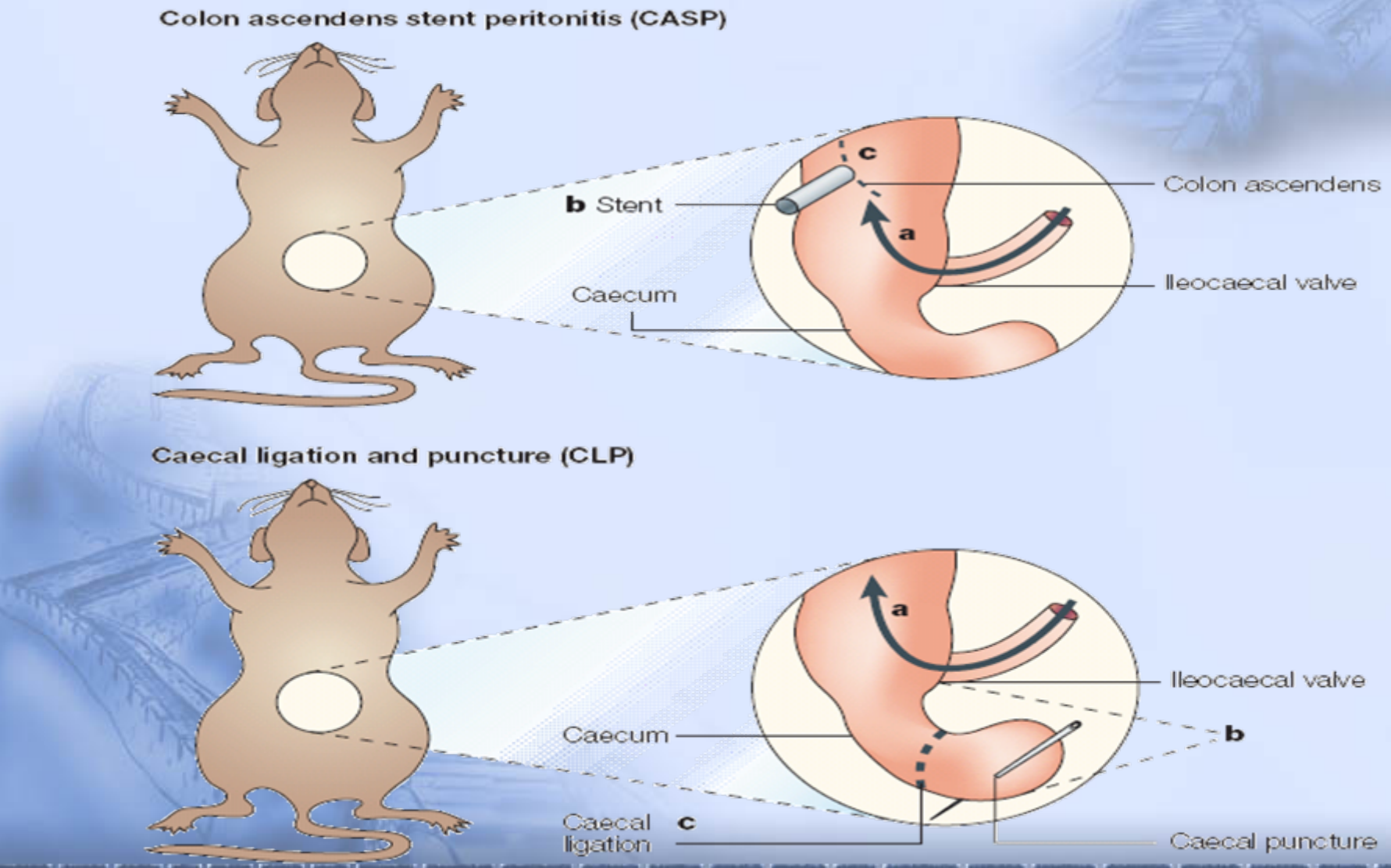
Human



Study Group	No. of Patients	No. of Deaths
Placebo (●)	33	10
0.15 mg/kg (○)	30	9
0.45 mg/kg (△)	29	14
1.5 mg/kg (□)	49	26

N Engl J Med. 1996 Jun 27;334(26):1697-702.

Host-barrier disruption models: CASP and CLP



Nat Rev Drug Discov. 2003; 2: 391-405.

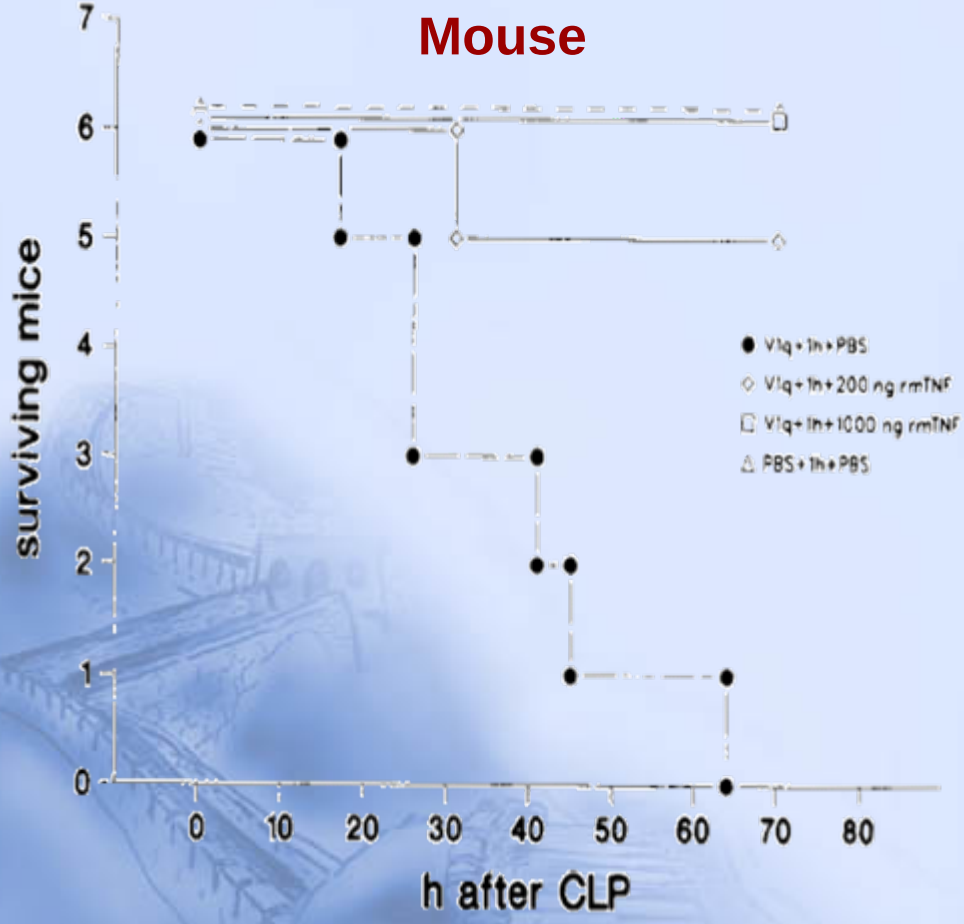
Variability factors of the model

- Needle size used for perforation
- Number of perforations
- Amount of caecum ligated/amount of necrosis induced
- Uncontrolled bacterial load (amount of stool milked into peritoneum)
- Sex, age and strain

J. Clin. Invest. 2009; 119:2868–2878. Nat Rev Drug Discov. 2003; 2: 391-405.

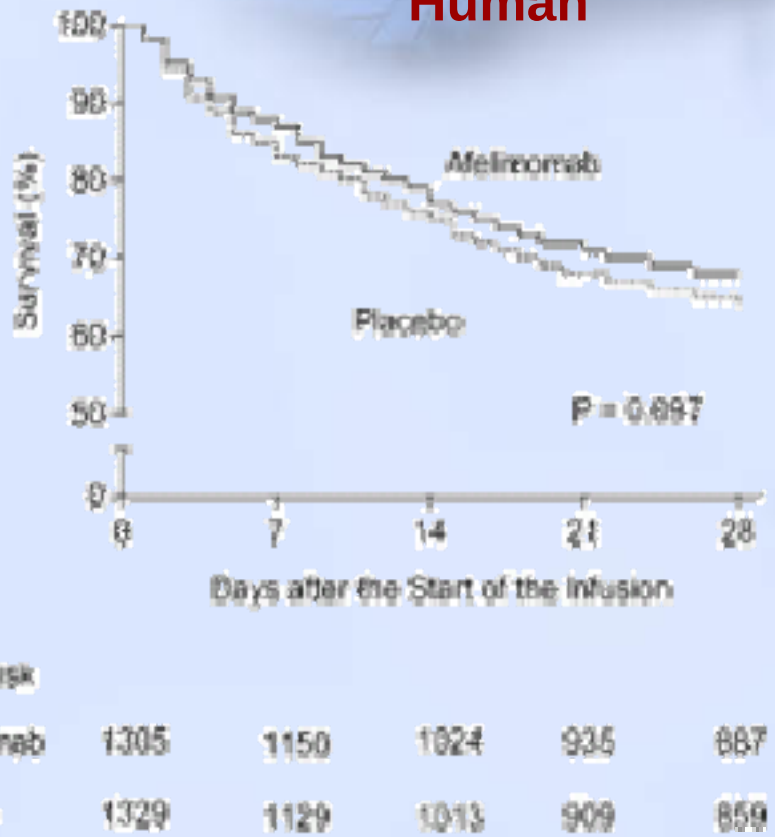
Similar results between CLP model and clinical trial of anti-TNF-a

Mouse



J Immunol. 1990 Dec 1;145(11):3762-6.

Human



Crit Care Med. 2004 Nov;32(11):2173-82.

Advantage and disadvantage of different models

Animal model	Advantage	Disadvantage
LPS injection	Simple, sterile; some similarities with human sepsis pathophysiology	Early and transient increases in inflammatory mediators more intense than in human sepsis
Bacterial infection	Early hyperdynamic state	No change in intrarenal microcirculation; biosafty consideration
CLP and CASP	Early silent period; moderate and delayed peak of mediators; multiple bacterial flora	Age and strain variability; early hemodynamic period in some models

J. Clin. Invest. 2009; 119:2868–2878.

Problems of current models

- **A mouse is not a man**
- **Is the model of sepsis related to the clinical situation in humans?**
- **The model takes no account of human variability**
- **…..**

J. Clin. Invest. 2009; 119:2868–2878.

Thanks!!!