if Infektiologie Freiburg
beraten–behandeln–forschen

# Commensal Microbiota: The Good, the Bad, and The Ugly

*Johannes Huebner*
Division of Infectious Diseases
University Hospital Freiburg

# Case Report: KV *1939

- **06/10:** cardiac arrest with ventricular fibrillations, acute renal failure
- Echocardiogram: vegetations, in BC ***E. faecalis***
- **06/11:** initiation of ampicillin/sulbactam, no aminoglycoside b/o renal failure
- **06/17:** BC still positive for ***E. faecalis***, addition of ceftriaxon
- **06/18:** Patient complained about strong pain in lumbar region; CT Scan: suspicion of spinal osteomyelits
- Generalized exanthema, suspected penicillin hypersensitivity
- transfer to University Hospital Freiburg

# Case Report: KV *1939

- Switched to daptomycin (6 mg/kg/die), BC at admission still positive for ***E. faecalis***
- Subsequent BC 06/20 and 06/24 still positiv (i.e. after 3 weeks of antibiotic therapy !)
- 06/24: Switched to ampicillin 4 x 2 g and gentamicin 3 x 40 mg (improved renal function)
- BC 06/26 and 06/27 negative
- increasing valvular insufficiency, therefore 07/01 implantation of a artificial valve, explanted valve tissue culture-positive for ***E. faecalis***
- Subsequent treatment for another 14 days with ampicillin/genta followed by 4 weeks ampicillin i.v.

# Several Noteworthy Points:

- *E. faecalis* is a human commensal present in all of us
- Sometimes this usually benign commensal can transform into a life-threatening pathogen
- Molecular and epidemiological studies have so far not been able to identify specific virulence factors responsible for this transition
- A new paradigm is needed to explain and understand “opportunistic” infections

# Pathogenicity and Virulence

## Koch´s Postulates (1882):

1. Microbe must be associated with lesion
2. Bacteria must be isolated in pure culture
3. Isolated bacterium must cause disease when inoculated into humans or animals
4. Bacteria must be isolated from intentionally infected animals

# “Molecular” Koch´s Postulates

1. A gene (or its product) should be found only in bacterial strains that cause disease (and not in avirulent bacteria)
2. The gene should be isolated by cloning
3. Disrupting the gene in a virulent strain should reduce the virulence
4. Alternatively, introducing the cloned gene into an avirulent strain should render the strain virulent
5. It should be demonstrated that the gene is expressed by the bacterium when it is in an animal or human volunteer at some point during the infection

# Understanding Pathogenicity of “bona fide” Pathogens

- **Assumption:** Disease-causing bacteria have evolved specifically to cause human (or animal) disease
- Role of Yop proteins (T3SS) in the pathogenesis of Yersinia pestis
- Role of listeriolysin O in releasing phagocytosed Listeria from the phagosome into the cytoplasma
- Role of anthrax toxin (cell-binding protective antigen - PA, and two enzyme components, edema factor - EF and lethal factor - LF) in the pathogenesis of anthrax

# Problems with Koch´s Postulates

1. Microbe must be associated with lesion
   - some bacteria colonize without causing symptomatic disease
2. Bacteria must be isolated in pure culture
   - some bacteria cannot be cultivated
3. Isolated bacterium must cause disease when inoculated into humans or animals
   - disease too serious to use in human
   - no appropriate animal model exists
4. Bacteria must be isolated from intentionally infected animals
   - see above

# The Human-Microbe Interaction

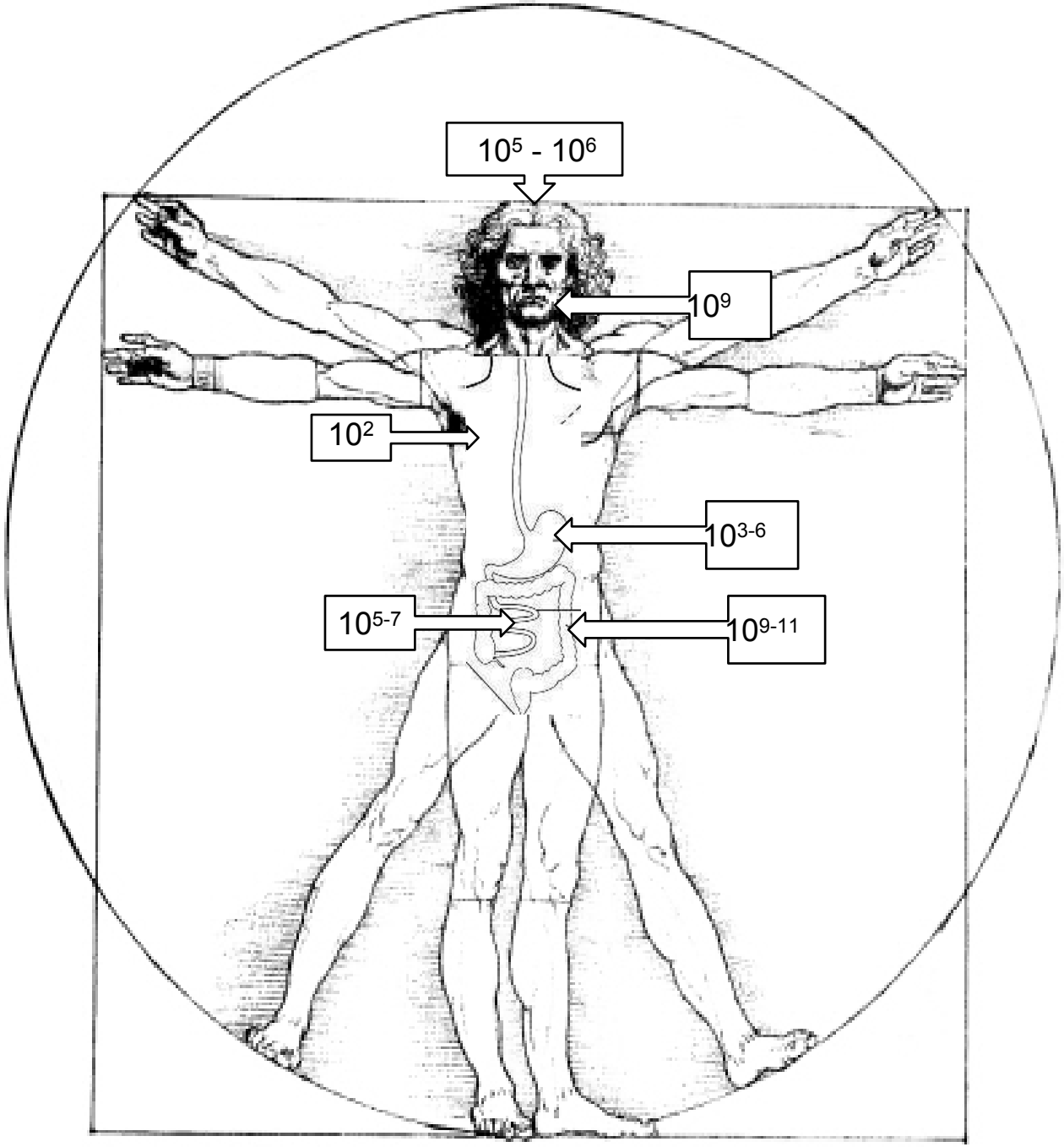
1. Not all people (hosts) are equal in their response to a specific microorganism
2. Not all strains of a bacterial species have equal ability to cause disease, even in a specific host setting
3. Disease symptoms result when equilibrium does not develop between disease-causing bacteria and humans
4. Most often, humans are accidental hosts of bacteria that normally occupy another ecological niche
5. A good parasite does not kill its host – **a peaceful coexistence is the rule** and disease is the exception !!

# Symbiosis

**Symbiosis is the persistent and intimate living together of dissimilarly named organisms.**

**Parasitism is the most popular and most exquisite phenomenon of symbiosis.**

**Anton Heinrich de Bary 1879**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# The Gastro-Intestinal Ecosystem

- No complex bacterial ecosystem has been completely analyzed so far
- The human GI tract is the most densely populated bacterial ecosystem on earth
- About 95-99% of the colonic flora are obligate anaerobes
- Many (most) species are not cultivable
- Huge differences between luminal and wall-adhering populations
- Antimicrobial peptides are secreted by Paneth cells or by other intestinal bacteria

**Jeffrey Gordon**

# Metagenomics

**Culture-independent** analysis of the composition and dynamic operations of microbial communities. This includes community characterization at the level of DNA (**microbiome**), RNA (**metatranscriptome**) and metabolic networks (**metabolome**).

# „Diversity of the Human Intestinal Microbial Flora“

- 395 bacterial phyla
- 1 archaea
- 62% new bacterial sequences
- 80% of species not cultivable
- mostly gram-positive bacteria (61% clostridia) and Bacteroides spp., only about 0,1% Proteobacteria
- 3 completely new lineages (between cyanobacteria und chloroplasts)

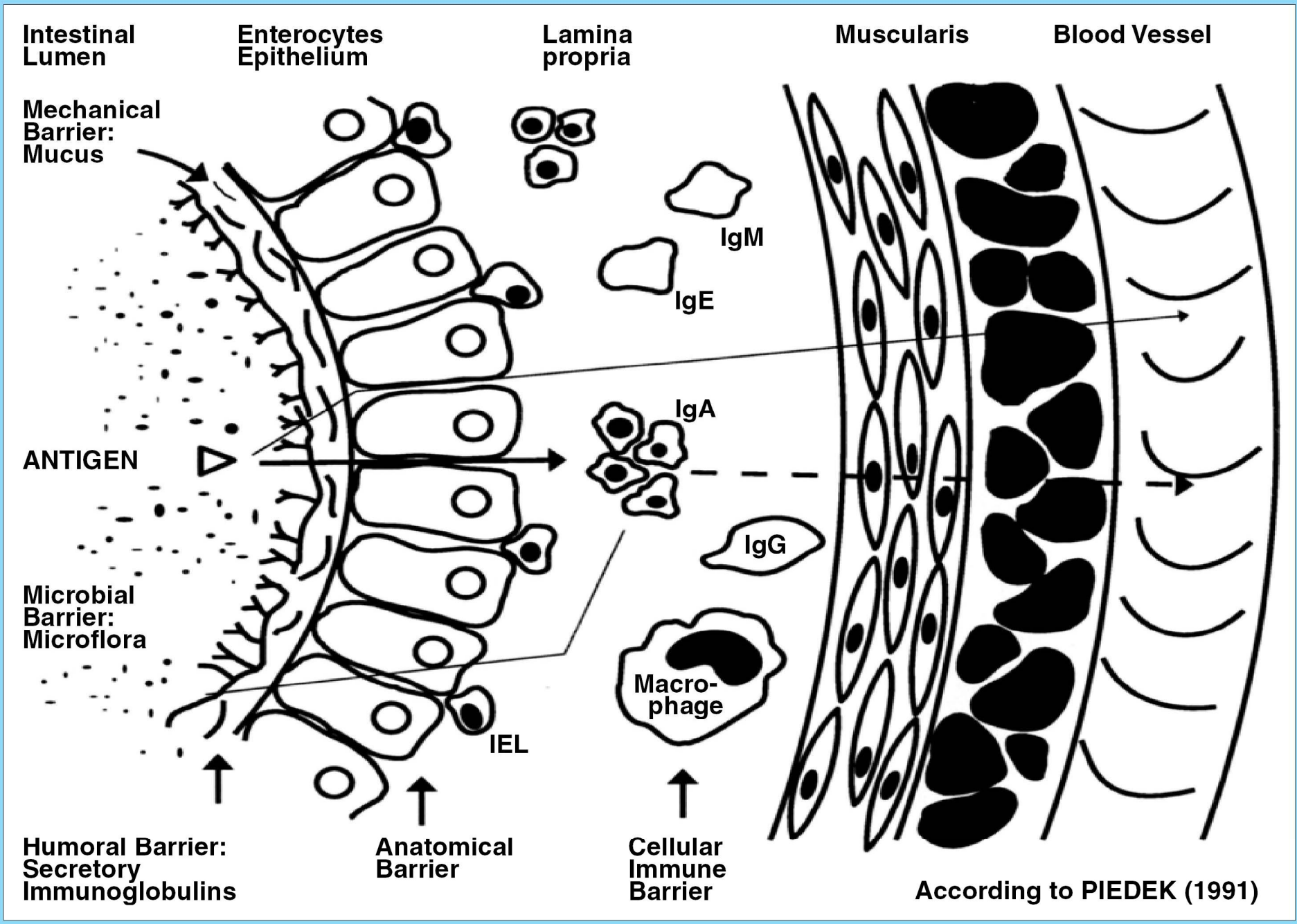
Science 308:1635-38;2005

A **microbiome** is the totality of microbes, their genetic elements (genomes), and environmental interactions in a defined environment (Joshua Lederberg)

Our "**microbiome**" contains about 100 times more genes then our genome

Humans are "superorganisms" whose metabolism is a combination of microbial and human metabolic pathways

Gill et al., Science 312:1355-1359;2006




# Mucosal Block

# Functions of the Physiological GI Flora

- Synthesis of vitamins (e.g. vitamin K)
- Metabolism of otherwise indigestible food components (e.g. plant carbohydrates)
- Colonization resistance
- Regulation of the intestinal angiogenesis and epithelial development
- Protection from inflammatory bowl disease
- Regulation of fat storage
- Development of the innate and adaptive immune system

# Symbiosis

## Parasitism

One partner is subject to harm while the other, the parasite, benefits. Nevertheless, the association is persistent

## Neutralism

No evident benefit or harm to either organism

## Commensalism

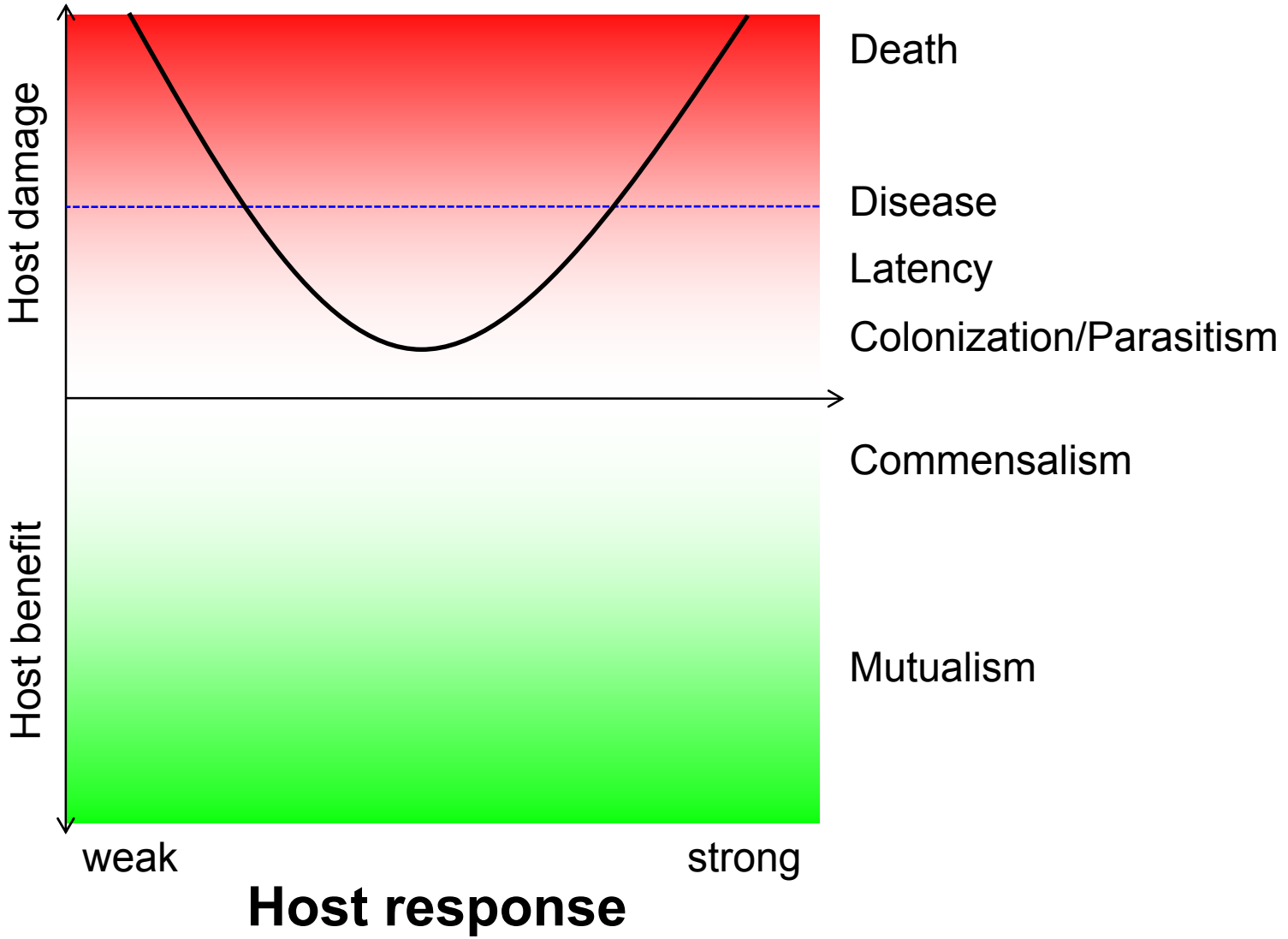
The benefit relation is one-sided, but without harm to either organism

## Mutualism

Both partners are benefited

Hans G. Schlegel 1992

# The Damage-Response Framework




Casadevall & Pirofski, Nat Rev Microbiol 2003

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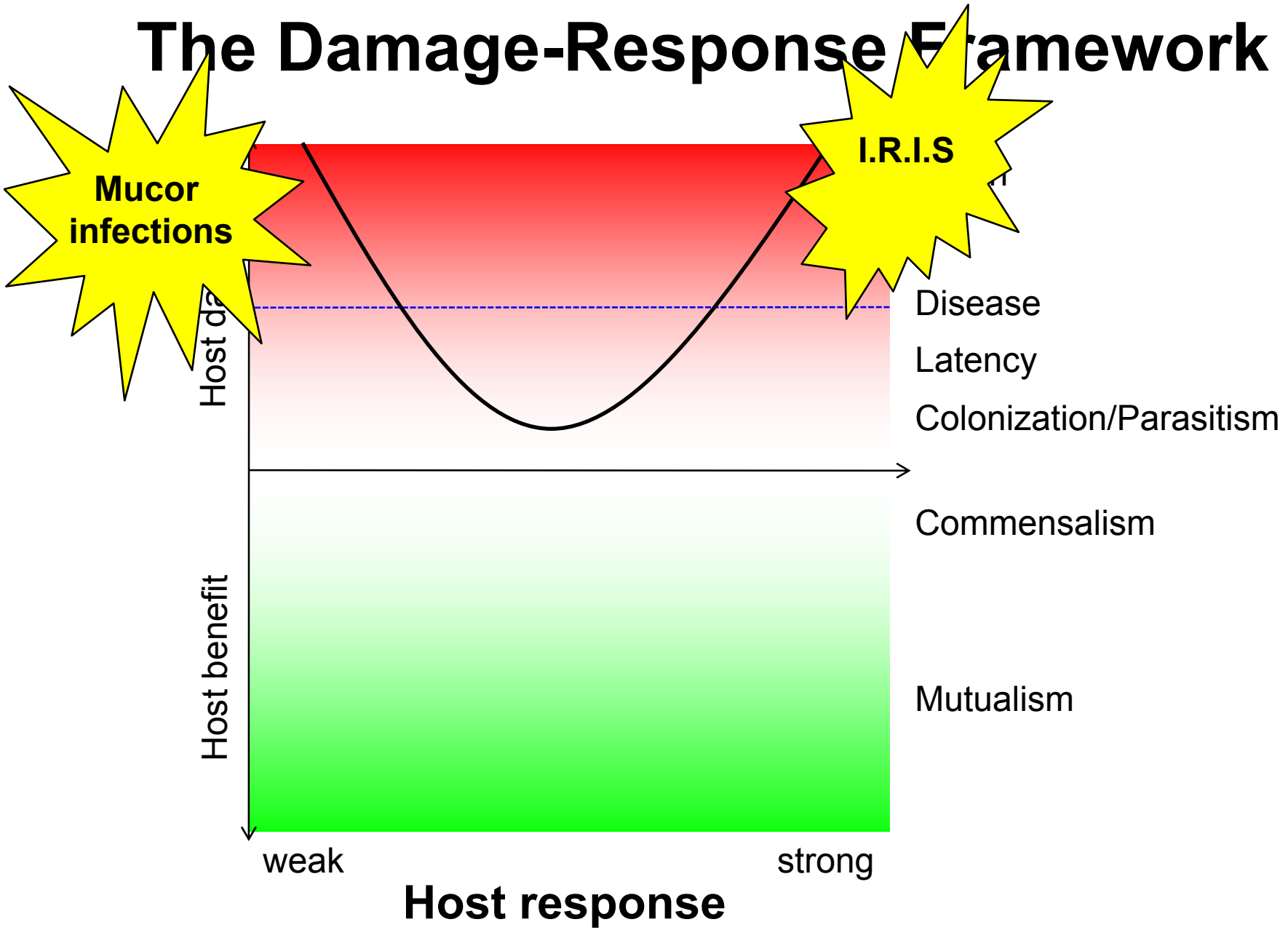


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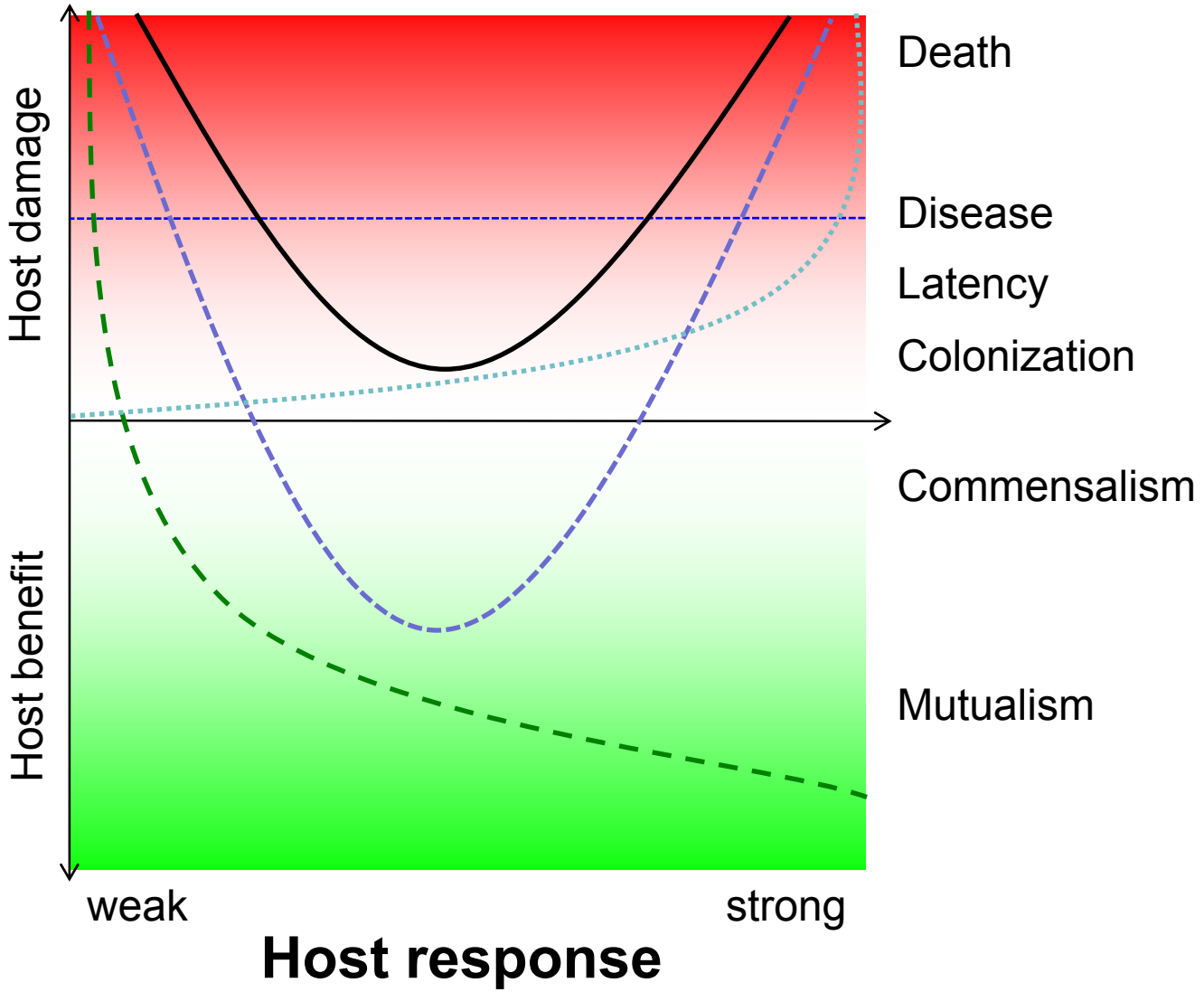


Casadevall & Pirofski, Nat Rev Microbiol 2003

# Tenets of the Damage-Response Framework

- Microbial pathogenesis is an outcome of an interaction between a host and a microorganism
- The host-relevant outcome is determined by the amount of damage to the host
- Host damage can result from microbial factors and/or the host response

# Conclusions

- Healthy individuals live with a plethora of commensal bacterial species
- Some of these are "beneficial" pathogens that can cause life-threatening disease under certain circumstances
- Traditional "pathogenicity" or "virulence" models fail to explain this transition
- Novel concepts, such as the Damage-Response Framework, may help to understand these complex interactions