



# Immune Reactions to Insect Bites and Stings

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# Disclosures

- None

# Objectives

- Identify the immunologic process causing inflammation after arthropod bites and stings
- Use the underlying immunologic process to select optimal treatment for insect bites and stings

# Inflammation

- Innate inflammatory responses
- Histamine-induced inflammation
- Th-1 induced inflammation
- Th-2 induced inflammation
- Th-17 induced inflammation

# Innate inflammation



# Innate inflammation



# Innate inflammation



# Inflammation

- Innate inflammatory responses: Gets better over days



Ichneumon wasp  
© Tom Murray



Corsair bug  
© Sharon Moorman

Punctures from:

Stings: solitary wasps, solitary bees

Bites: true bugs, lacewing larvae, thrips, centipedes, spiders, flies





# “Spider bite” epidemics

- Family complains of spider bites developing over successive nights
- Several new lesions noted most mornings
- Each lesion progressively more painful over several days
- Spiders of various sorts seen in the home; no witnessed bites



# MRSA epidemics

- Family complains of spider bites developing over successive nights
- Several new lesions noted most mornings
- **Each lesion progressively more painful over several days**
- Spiders of various sorts seen in the home; no witnessed bites



# Inflammation

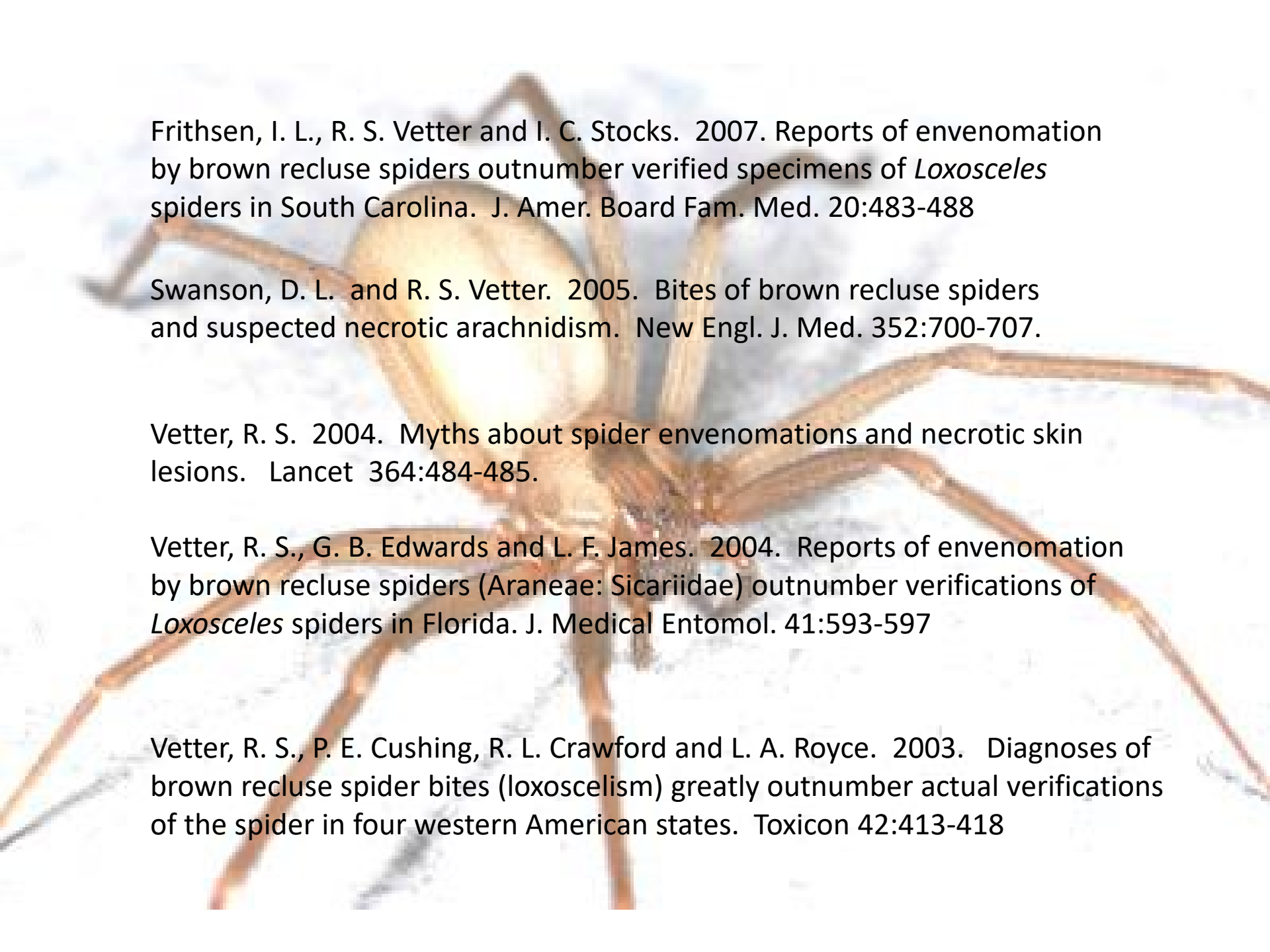
- Innate inflammatory responses: **Pain**, gets **better over days**
- Histamine induced inflammation
- Th-1 induced inflammation
- Th-2 induced inflammation
- Th-17 induced inflammation: **Pain**, gets **worse over days**

# Inflammation

**Mechanical injury, venom**

- Innate inflammatory responses: **Pain**, gets **better over days**
- Histamine induced inflammation
- Th-1 induced inflammation
- Th-2 induced inflammation
- Th-17 induced inflammation: **Pain**, gets **worse over days**

**Bacteria**



Frithsen, I. L., R. S. Vetter and I. C. Stocks. 2007. Reports of envenomation by brown recluse spiders outnumber verified specimens of *Loxosceles* spiders in South Carolina. J. Amer. Board Fam. Med. 20:483-488

Swanson, D. L. and R. S. Vetter. 2005. Bites of brown recluse spiders and suspected necrotic arachnidism. New Engl. J. Med. 352:700-707.

Vetter, R. S. 2004. Myths about spider envenomations and necrotic skin lesions. Lancet 364:484-485.

Vetter, R. S., G. B. Edwards and L. F. James. 2004. Reports of envenomation by brown recluse spiders (Araneae: Sicariidae) outnumber verifications of *Loxosceles* spiders in Florida. J. Medical Entomol. 41:593-597

Vetter, R. S., P. E. Cushing, R. L. Crawford and L. A. Royce. 2003. Diagnoses of brown recluse spider bites (loxoscelism) greatly outnumber actual verifications of the spider in four western American states. Toxicon 42:413-418

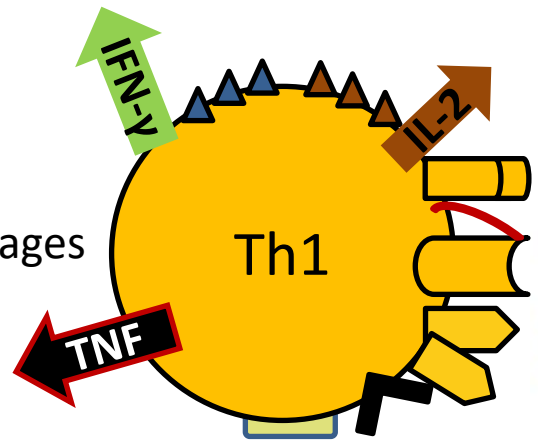
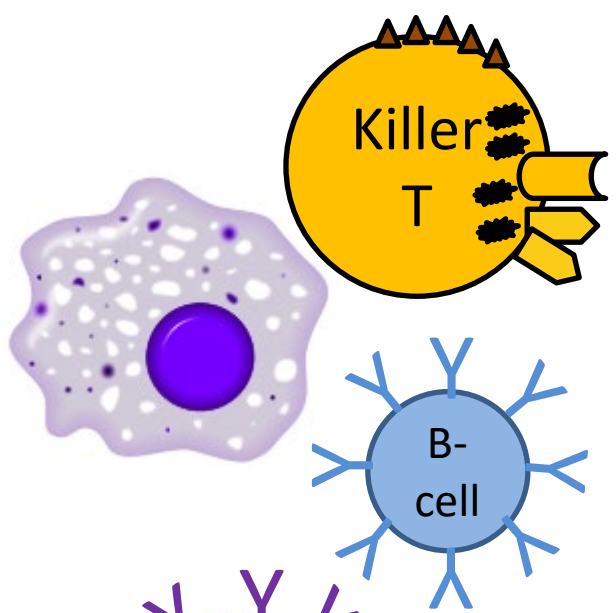
# Inflammation

**Mechanical injury, venom**

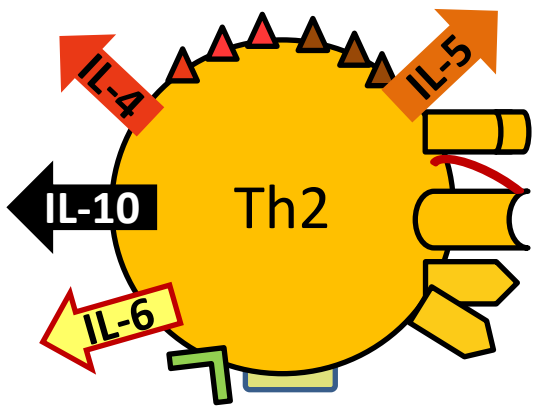
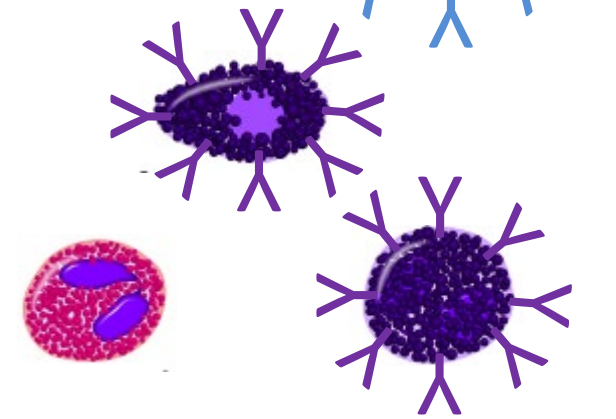
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**Bacteria**

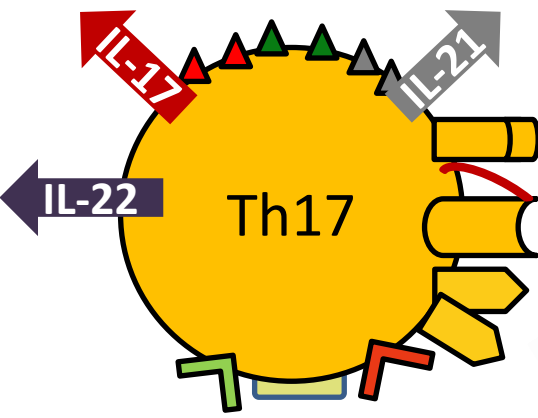
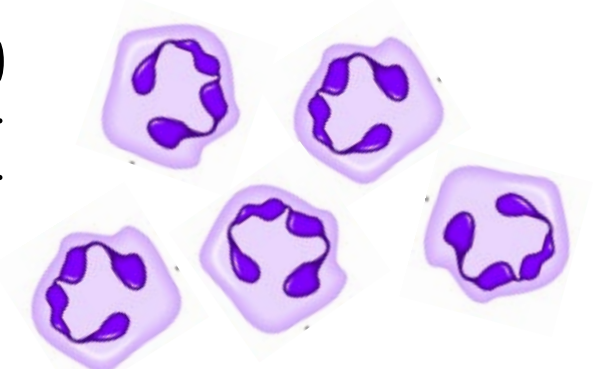
Pain, Sickness behavior from macrophages



Itch, Allergic inflammation



Pain, Pyogenic inflammation



# The adaptive immune system tailors its response to the type of threat

|              |                 |      |
|--------------|-----------------|------|
| • Virus:     | 0.01 $\mu$ m    | Th1  |
| • Bacterium: | 1 $\mu$ m       | Th17 |
| • Helminth:  | 100 $\mu$ m     | Th2  |
| • Mite:      | 1,000 $\mu$ m   |      |
| • Tick:      | 100,000 $\mu$ m |      |

# What keeps biting my daughter?

- Itchy red bumps develop on toddler's legs...  
... every Monday morning
- Clusters of lesions develop gradually over one to two days, persist for a week.
- Lesion onset is at times with no obvious exposure to arthropods, e.g. school.
- Antihistamines don't help

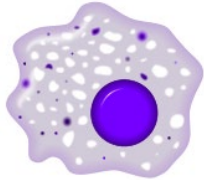
# Delayed-type hypersensitivity



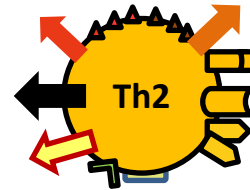
Tissue



Macrophage

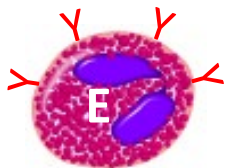


Lymph nodes

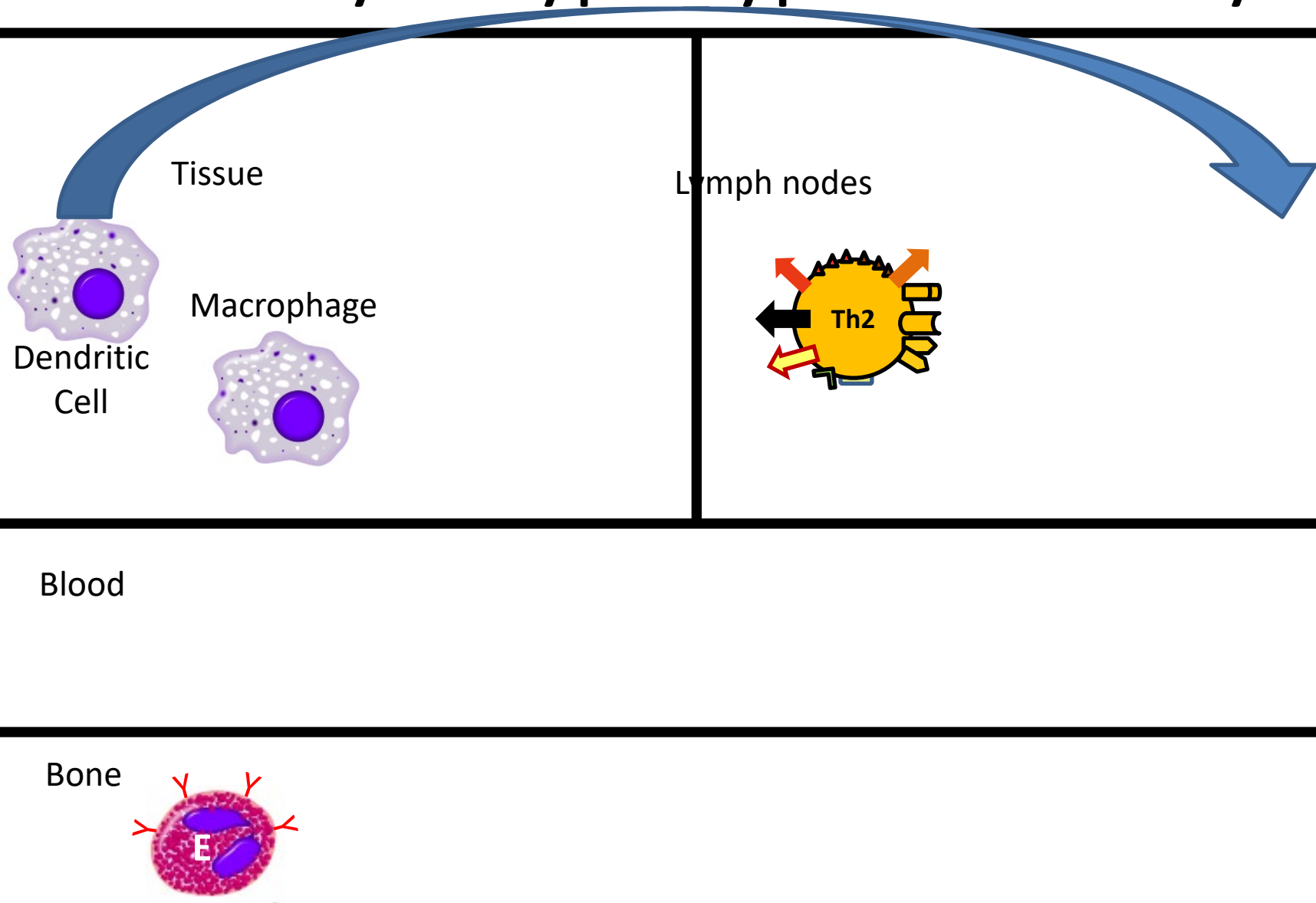


Blood

Bone



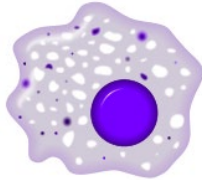
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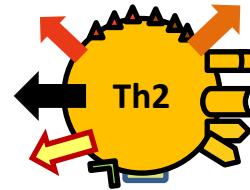
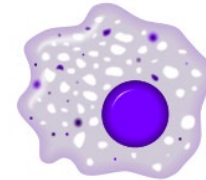
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Tissue

Macrophage



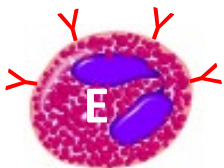
Lymph nodes



Dendritic  
Cell

Blood

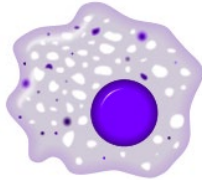
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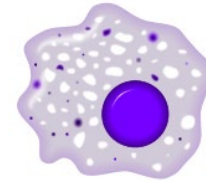
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Tissue

Macrophage

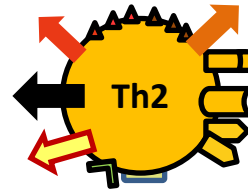


Lymph nodes

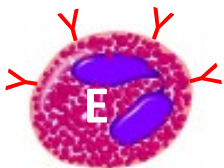


Dendritic  
Cell

Blood



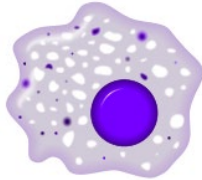
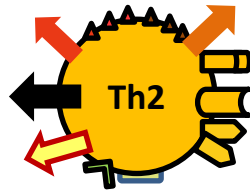
Bone



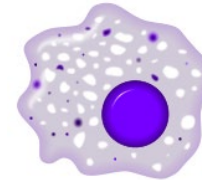
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Macrophage



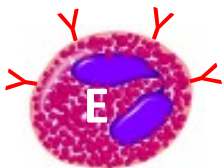
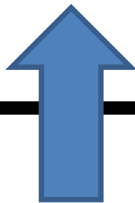
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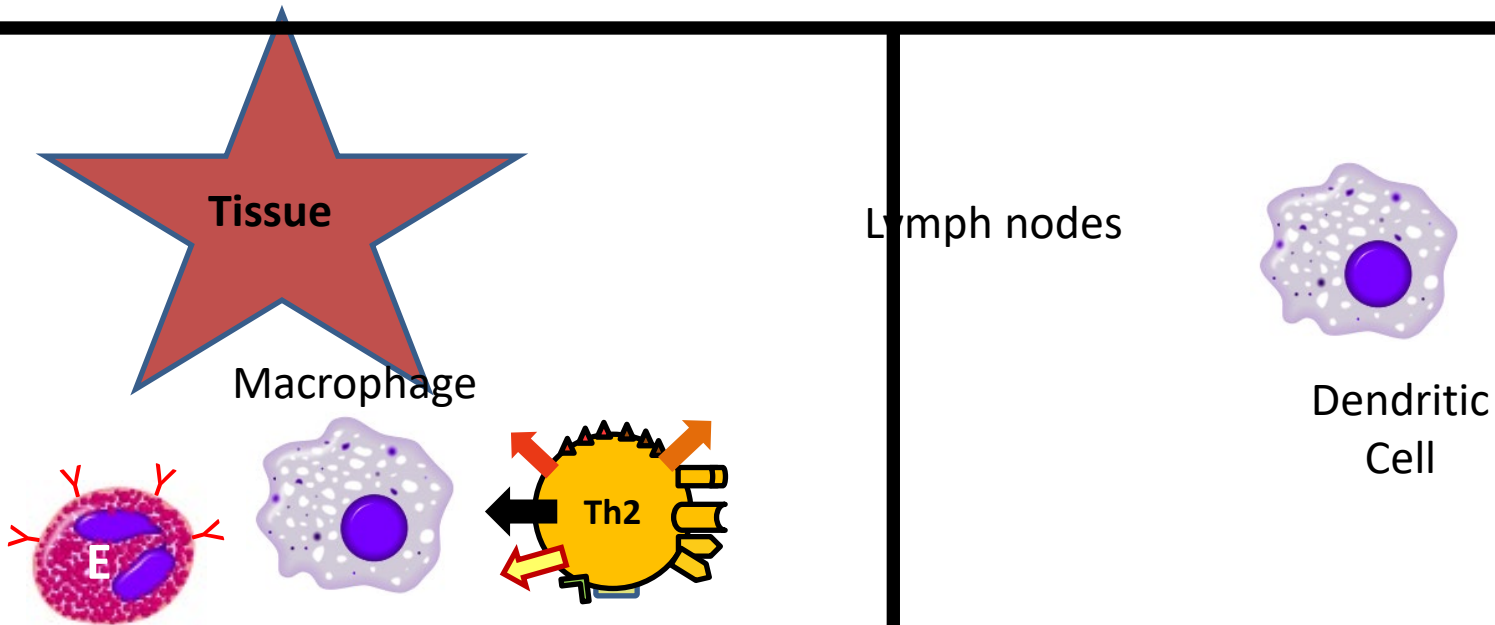
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Cell

Blood

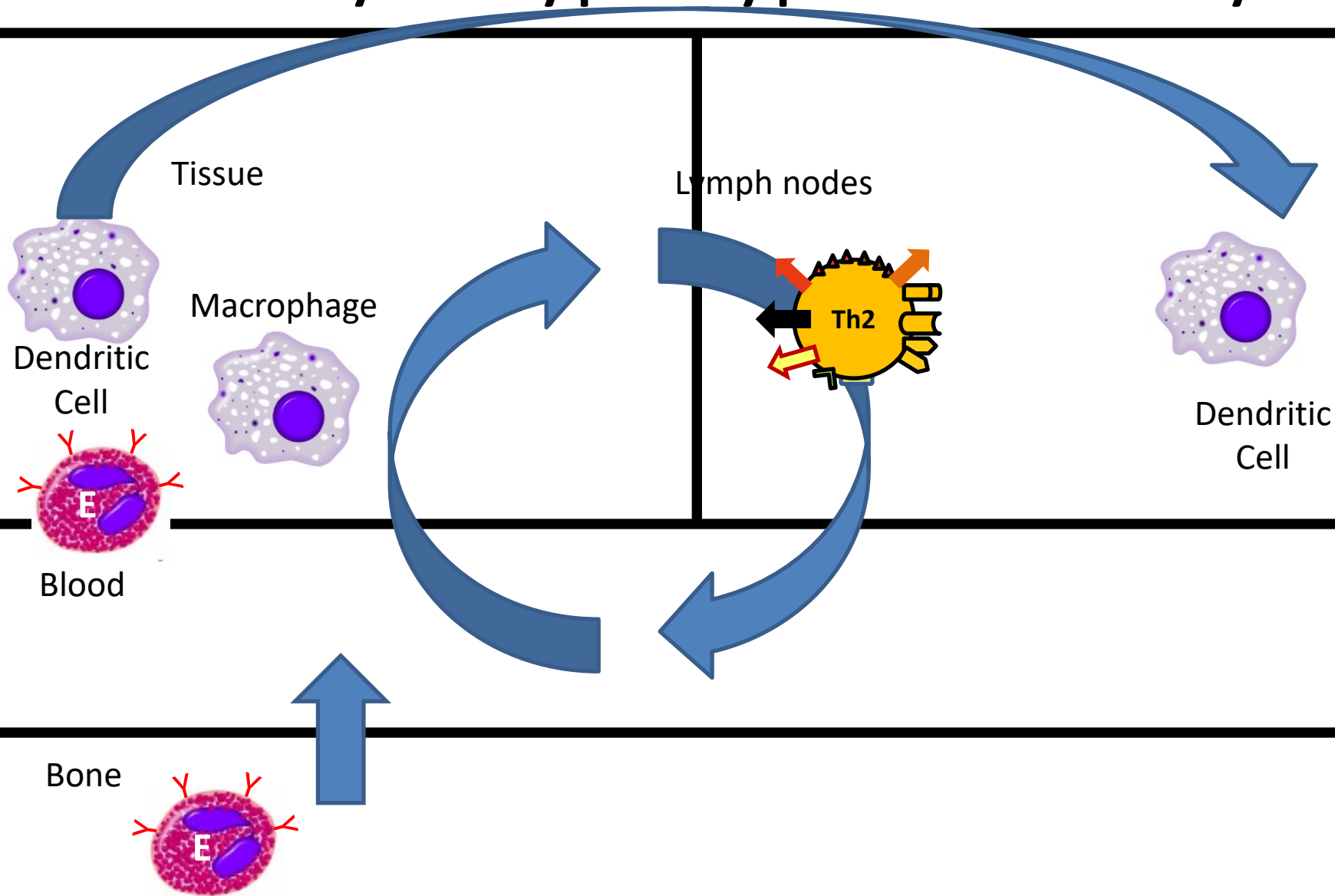
Bone



# Delayed-type hypersensitivity



# Delayed-type hypersensitivity



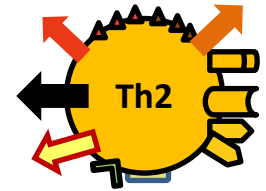
# What keeps biting my daughter?

- Delayed-type hypersensitivity from bites
  - Mosquitoes
  - Bed bugs
  - Chiggers

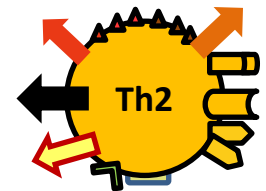




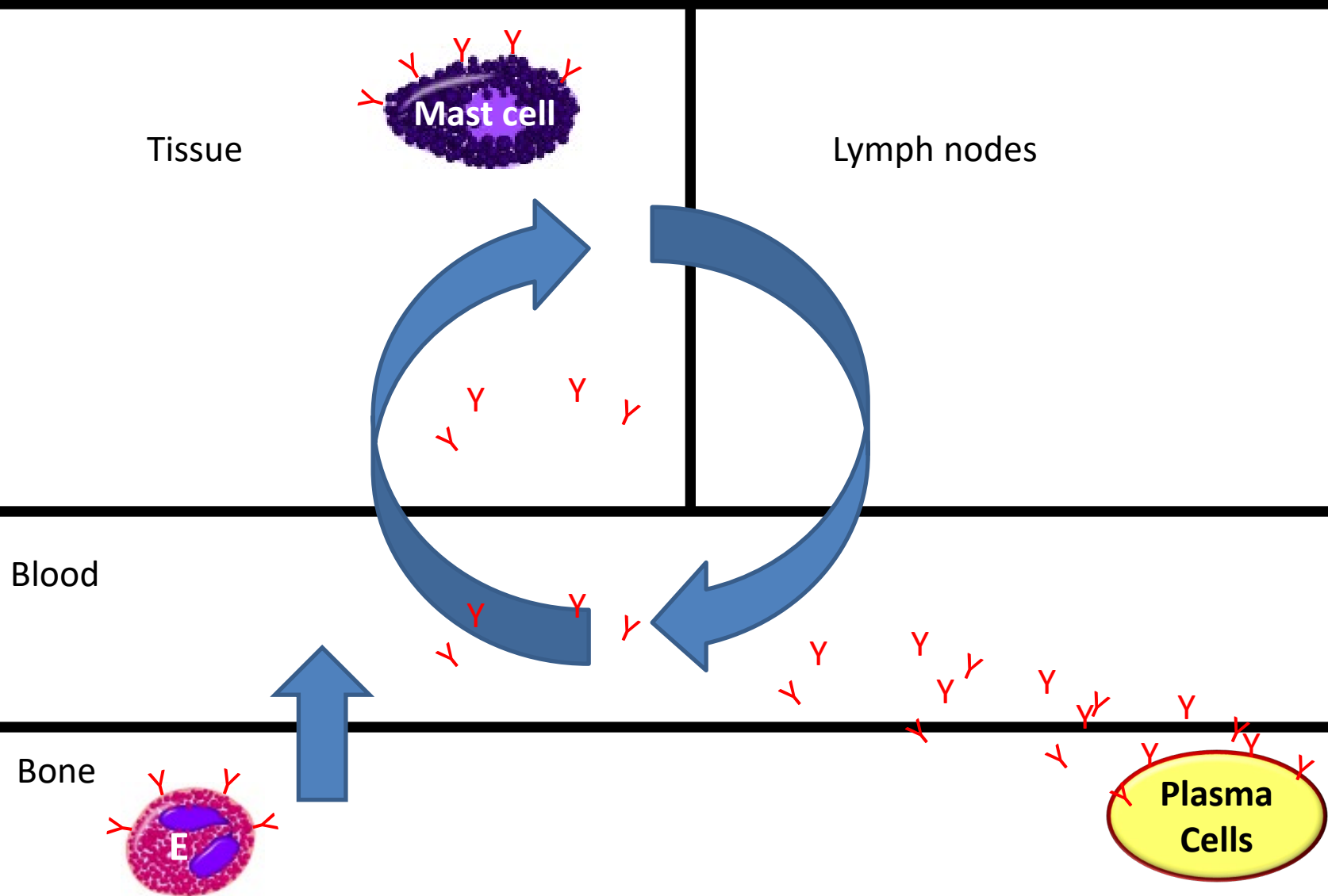
Large reactions with fever:  
Skeeter Syndrome



Blistering reactions:  
lymphoma  
celiac  
recent anaphylaxis



# Immediate-type hypersensitivity







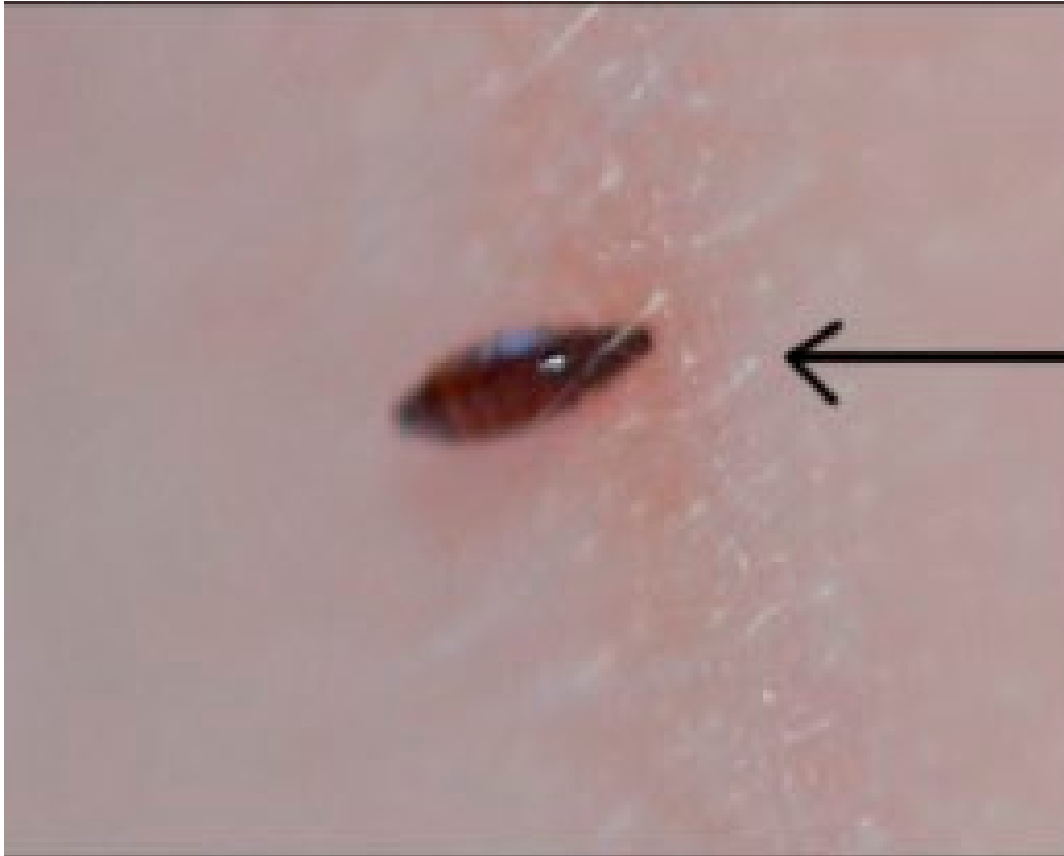
## Implications of allergic inflammation after arthropod bites or stings

| Stage of allergic sensitization | Immediate reaction                           | Delayed reaction                         | Implication                   |
|---------------------------------|----------------------------------------------|------------------------------------------|-------------------------------|
|                                 | Begins within minutes<br>Ends within 2 hours | Begins in 6-72hrs<br>Lasts days or weeks |                               |
| 1                               | Absent                                       | Absent                                   | No previous contact           |
| 2                               | Absent                                       | Present                                  | Few previous encounters       |
| 3                               | Present                                      | Present                                  | Multiple previous encounters  |
| 4                               | Present                                      | Absent                                   | Many previous encounters      |
| 5                               | Absent                                       | Absent                                   | Very many previous encounters |

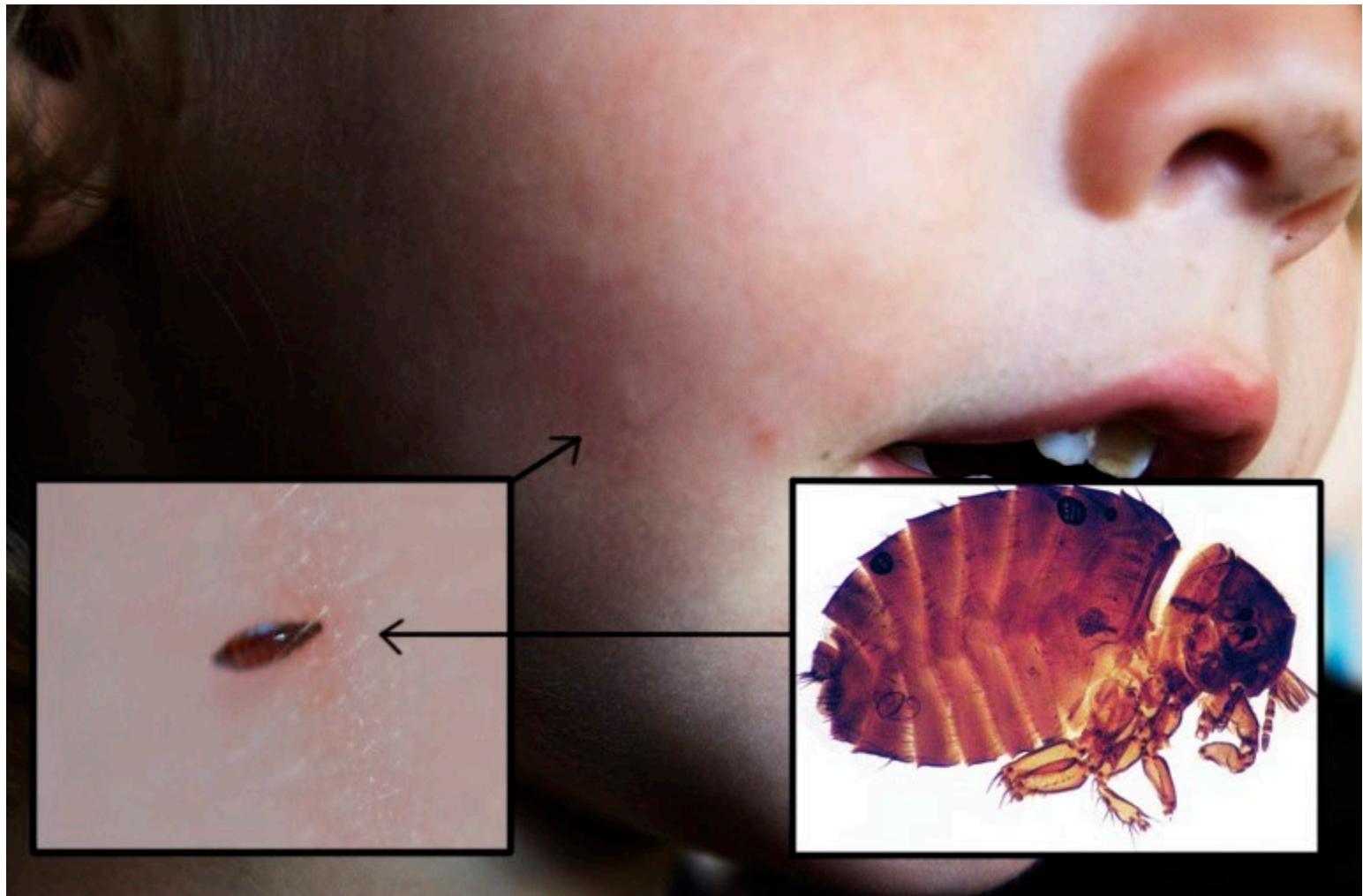
Mellanby K. Man's reaction to mosquito bites. *Nature*. 1946;158:554.

Feingold BF, Benjamini E, Michaeli D. The allergic response to insect bites. *Annu Rev Entomol*. 1968;13:137-158.





Carlson JC, Fox MS. A sticktight flea removed from the cheek of a two-year-old boy from Los Angeles. Dermatol Online J. 2009. 15(1):4.



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## Common human ectoparasites in the US

| Association    | Major groups  | Example species          |
|----------------|---------------|--------------------------|
| Fly to human   | Mosquitoes    | <i>Culex pipiens</i>     |
|                |               | <i>Aedes albopictus</i>  |
| Crawl to human | Bugs          | <i>Cimex lectularius</i> |
| Live on human  | Lice          | <i>Pediculus humanus</i> |
|                |               | <i>Phthirus pubis</i>    |
|                | Scabies mites | <i>Sarcoptes scabiei</i> |

## Common zoonotic ectoparasites in the US that bite humans

| Association     | Major groups       | Example species                                        |
|-----------------|--------------------|--------------------------------------------------------|
| Fly to animal   | Mosquitoes         | <i>Aedes vexans</i> (Floodwater mosquito)              |
|                 |                    | <i>Culiseta inornata</i> (Winter mosquito)             |
|                 | Other biting flies | <i>Culicoides variipennis</i> (No-see-um)              |
|                 |                    | <i>Chrysops niger</i> (Deer fly)                       |
| Crawl to animal | Ticks              | <i>Amblyomma americanum</i> (Lone star tick)           |
|                 | Mites              | <i>Trombicula alfreddugesi</i> (Harvest mite/chigger)  |
|                 | Fleas              | <i>Ctenocephalides felis</i> (Cat flea)                |
|                 |                    | <i>Echidnophaga gallinacea</i> (Sticktight flea)       |
| Live on animal  | Mites              | <i>Sarcoptes scabiei</i> var <i>canis</i> (mange mite) |

# Itch-Scratch Reflex





# What good are mast cells?

- Tick-borne infection study group
  - Likelihood of Lyme disease infection decreased with >3 reports of tick-associated itch
  - Odds ratio 0.14,  $p = 0.01$ ; 95% CI: 0.94-0.03
- Venom morbidity and mortality
  - Snake and honeybee venoms tested on mice
  - Mast cell proteases degrade venom components



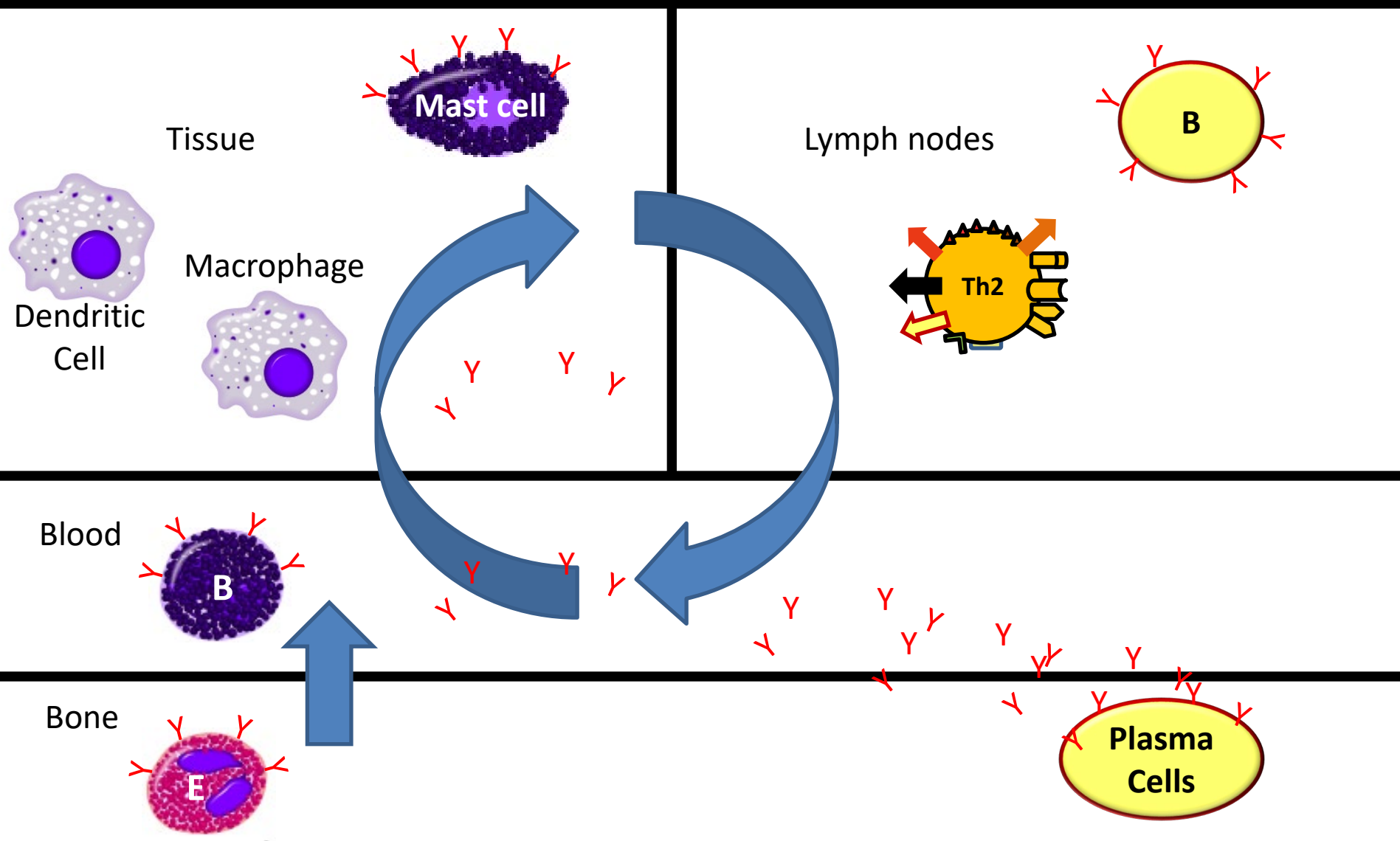
Burke G, et al. 2005. Hypersensitivity to Ticks and Lyme Disease Risk. *Emerging Infectious Diseases*. 11(1): 36-41.

Metz M, et al. 2006. Mast cells can enhance resistance to snake and honeybee venoms. *Science*. 313(5786):526-30.



Disseminated scabies in chemotherapy-induced immunosuppression

# The Allergic Immune System



# Inflammation

- Innate inflammatory responses: **Pain**
- Histamine induced inflammation: **Itch**
- Th-2 induced inflammation: **Itch**
- Th-17 induced inflammation: **Pain**

# Inflammation

- Innate inflammatory responses: **Pain**, gets better over days
- Histamine induced inflammation: **Itch**, gets better over hours
- Th-2 induced inflammation: **Itch**, gets worse over days
- Th-17 induced inflammation: **Pain**, gets worse over days

# Inflammation

- Innate inflammatory responses: **Pain**, gets better over days  
Time
- Histamine induced inflammation: **Itch**, gets better over hours  
Antihistamine
- Th-2 induced inflammation: **Itch**, gets worse over days  
Corticosteroids
- Th-17 induced inflammation: **Pain**, gets worse over days  
Antibiotic

# Inflammation

- Innate inflammatory responses: **Pain**, gets better over days  
Time, **reassurance, hugs, stickers**
- Histamine induced inflammation: **Itch**, gets better over hours  
Antihistamine, **insect repellent**
- Th-2 induced inflammation: **Itch**, gets worse over days  
Corticosteroids, **insect repellent**
- Th-17 induced inflammation: **Pain**, gets worse over days  
Antibiotic, **reassurance, hugs, stickers**

# Anaphylaxis

| Reaction time of minutes to several hours after trigger: | Criteria:                                                                                                               |
|----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| 1: Unlikely trigger                                      | <u>Must have</u> <b>Mucocutaneous</b><br>And<br><b>Respiratory</b> <u>or</u><br><b>Cardiovascular</b>                   |
| 2: Likely trigger                                        | <u>Any two of:</u><br><b>Mucocutaneous,</b><br><b>Respiratory,</b><br><b>Cardiovascular,</b><br><b>Gastrointestinal</b> |
| 3: Known trigger (for this patient)                      | <b>↓ BP:</b><br>Age specific or <30 below baseline systolic                                                             |

## Organ system signs:

### Mucocutaneous:

diffuse hives, pruritus, flushing; swollen lips, tongue, uvula

**Respiratory:** dyspnea, wheeze-bronchospasm, stridor, ↓ PEF, hypoxemia

**Cardiovascular:**  
↓ BP, hypotonia, syncope, incontinence

**Gastrointestinal:**  
Persistent crampy abdominal pain, vomiting

# With a diagnosis of anaphylaxis...

- Prescribe epinephrine autoinjectors
- Teach them how to use the autoinjectors
- Teach them when to use the autoinjectors
  - Intranasal epinepheline is coming!
- Please refer to allergy (high risk clinic)

# Treating venom-induced anaphylaxis

- Ultrarush induction: 10 injections over 4 hours
- Monthly injection for 6 months
- Every 6-8 weeks to 5 years
- Protected after the ultrarush day
- 80% cure rate after 5 years
- Those not cured, reactions are better



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