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Immunotoxicology

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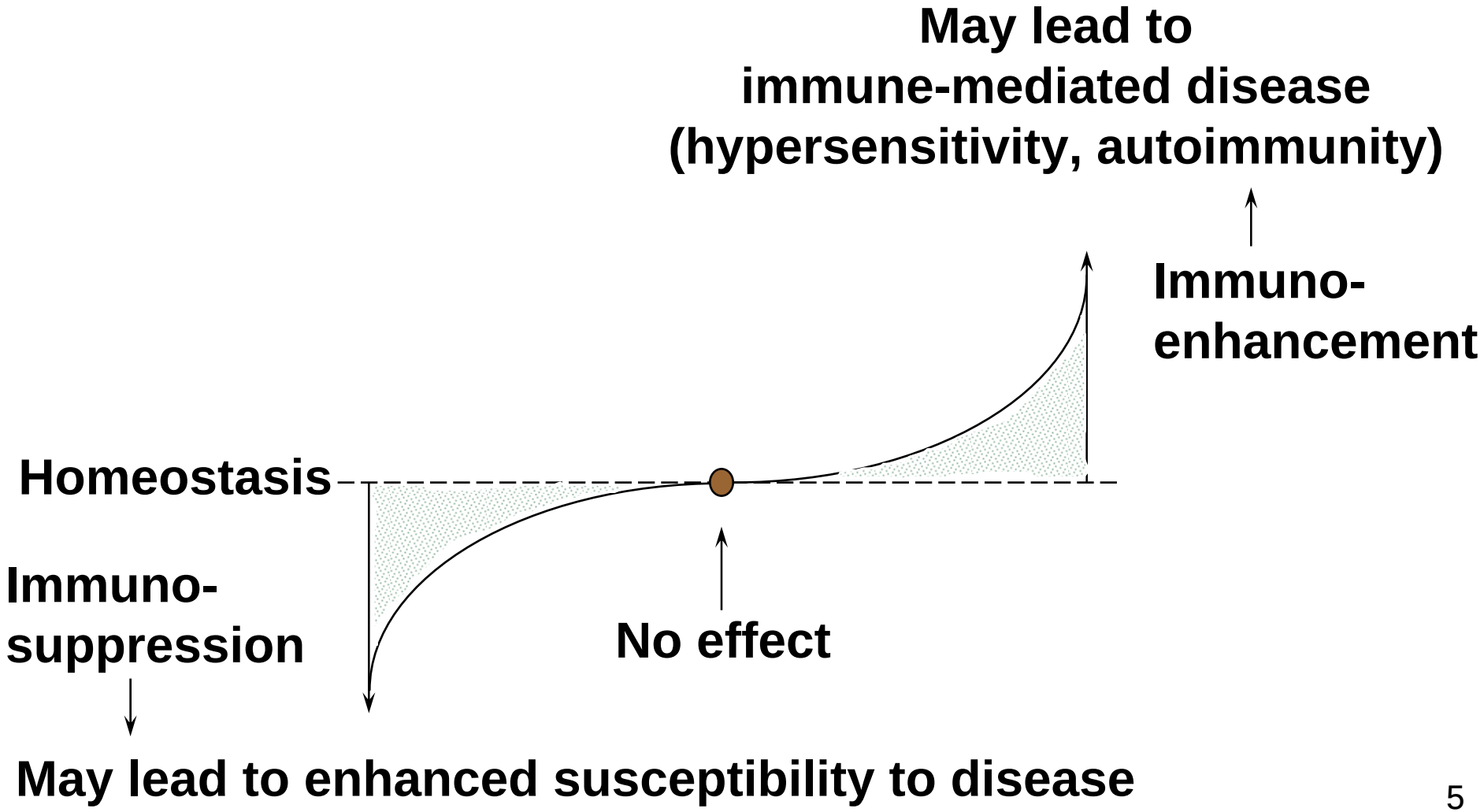
Section A

Overview of Immunotoxicology

Definition

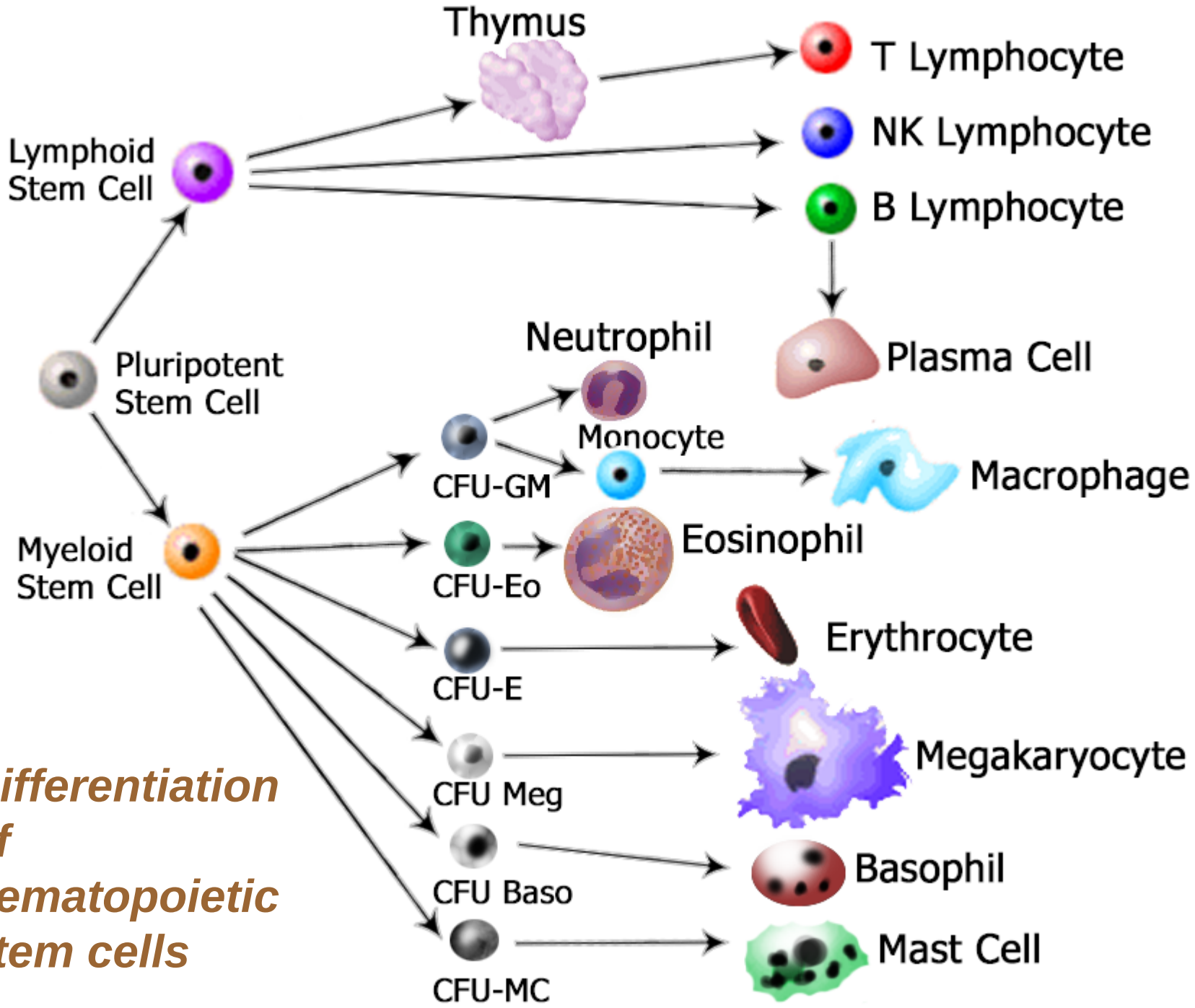
- **Immunotoxicology** is an adverse or inappropriate change in the structure or function of the immune system after exposure to a foreign substance (xenobiotic)

Potential Effects of Chemical Exposure on Immunological Function



Cardinal Characteristics of the Immune System

- Specificity
- Memory
- Ability to distinguish self from non-self



Differentiation of hematopoietic stem cells

Cytokines

- Molecular mediators of immune and inflammatory reactions
  - Interleukins
  - Interferons
  - Haemopoietic growth factors
  - Tumor necrosis factors
  - Transforming growth factors

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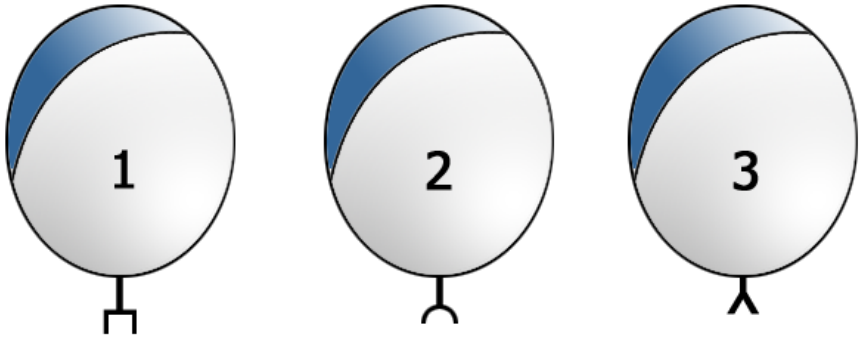
Section B

The Basics of an Immune Response

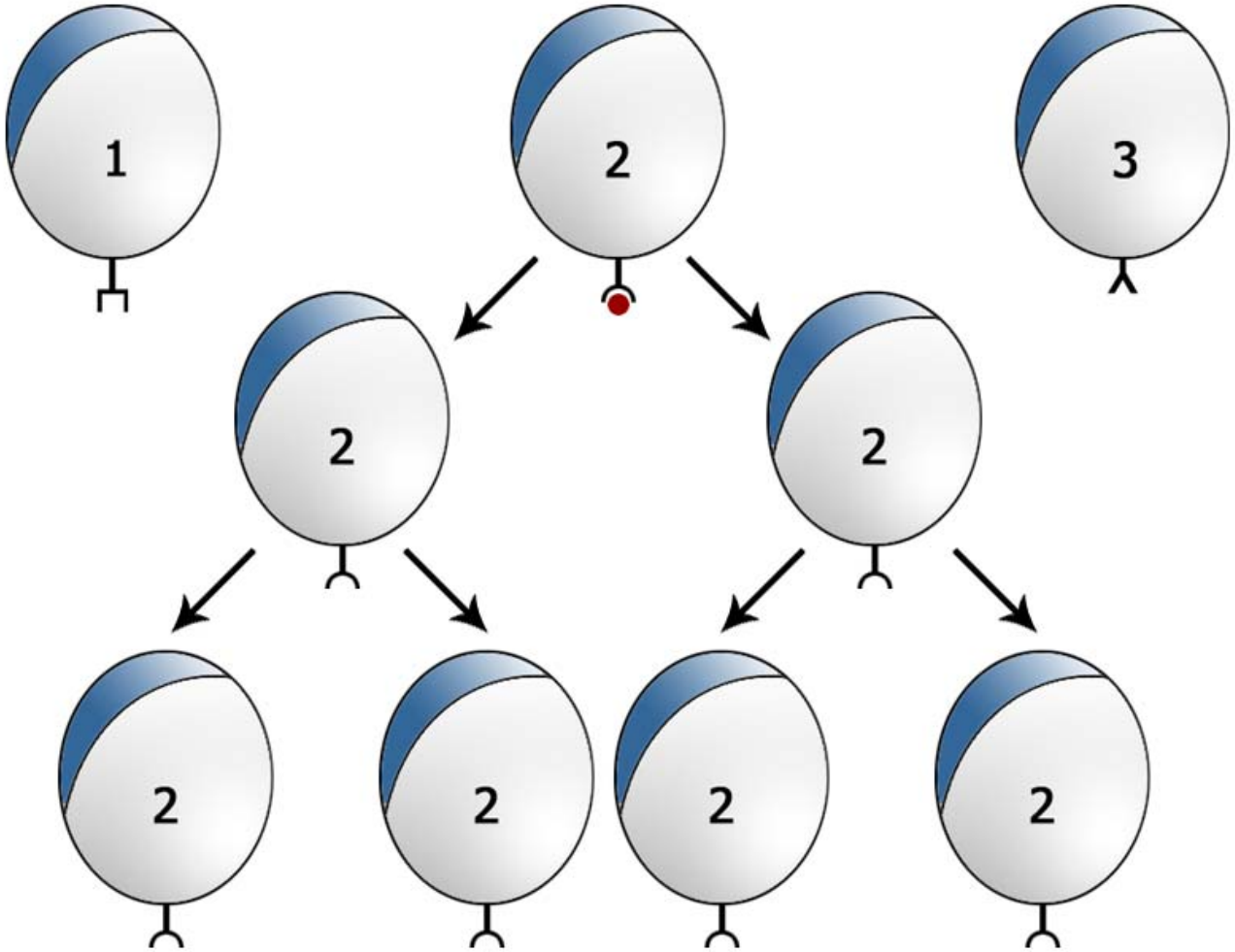
Lymphocyte Cloning

- **Lymphocytes** are clonally distributed with respect to antigen specificity
- Each clone of lymphocytes has unique membrane receptor for antigen



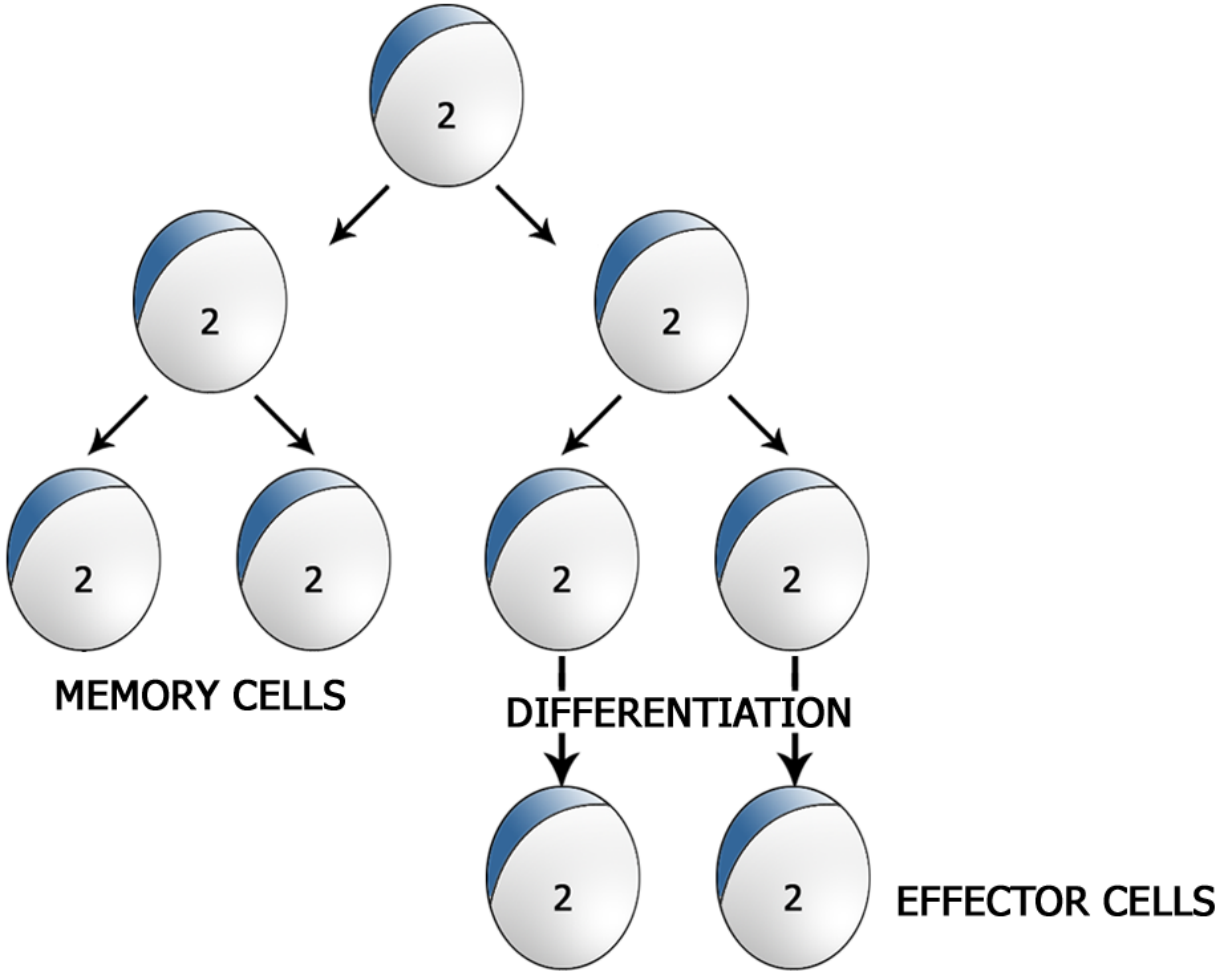
Interaction of Lymphocytes

With Antigen Results in Clonal Expansion



Daughter Cells Resulting from Clonal Expansion

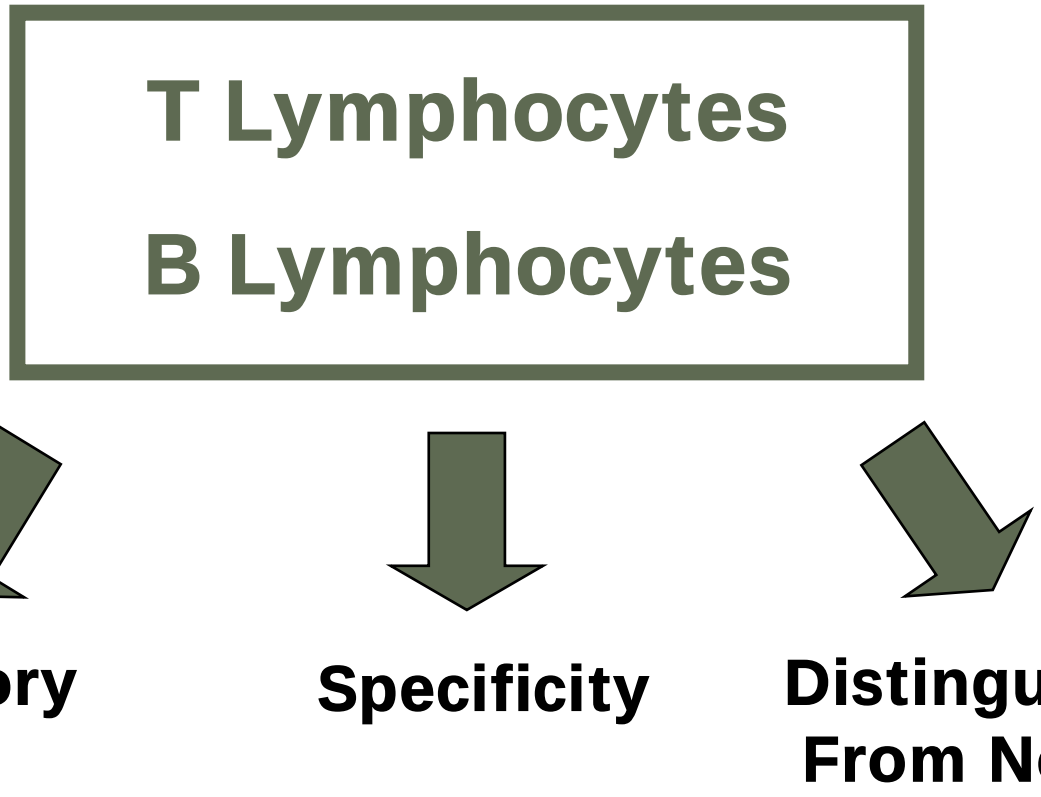
- They either remain as long-lived memory cells or differentiate into effector cells



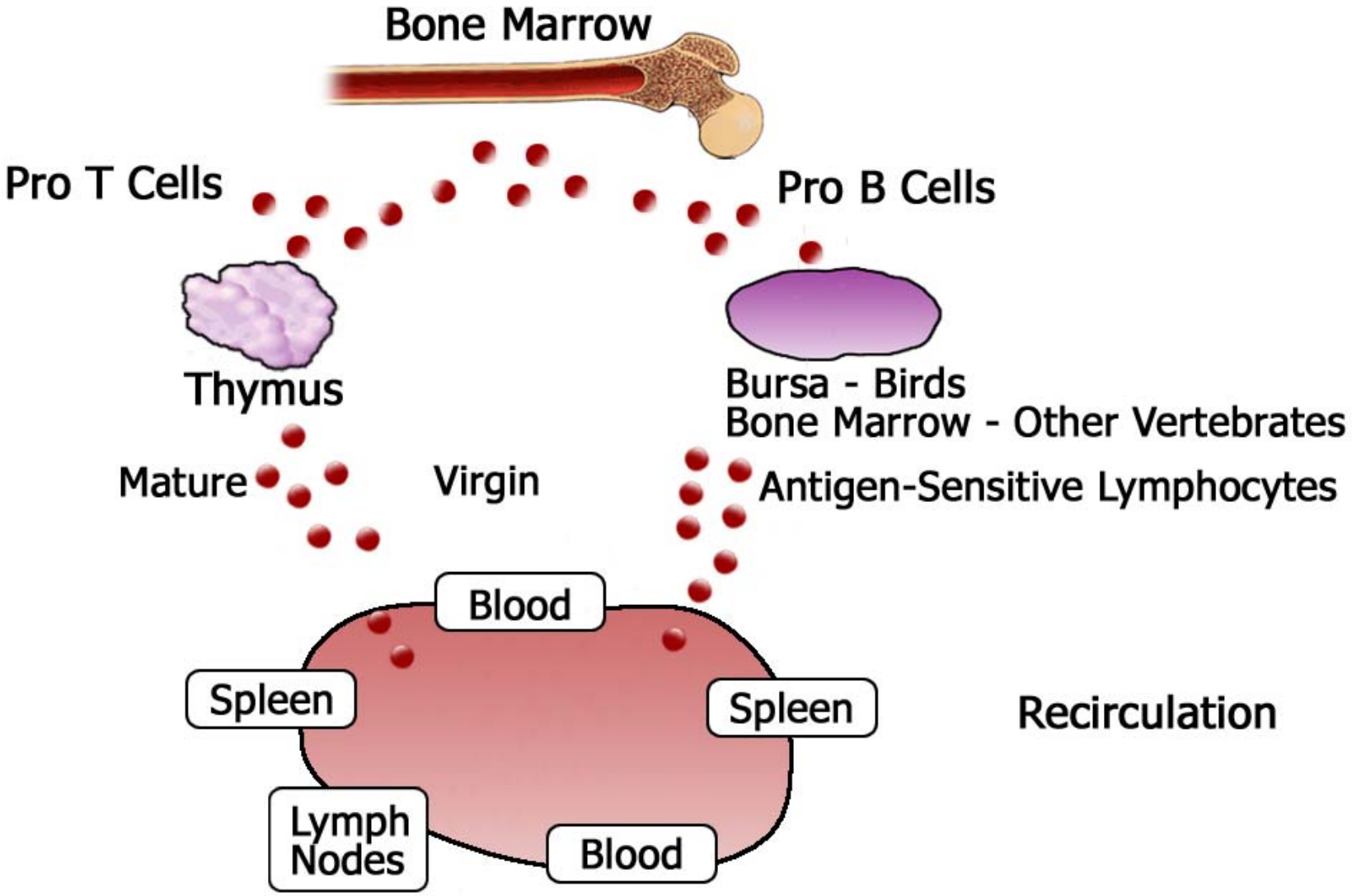
Memory Cells and Effector Cells

- **Memory cells**
  - Provide for an accelerated and more vigorous response following a second encounter with the same antigen
- **Effector cells**
  - Either directly or indirectly cause the elimination of antigen

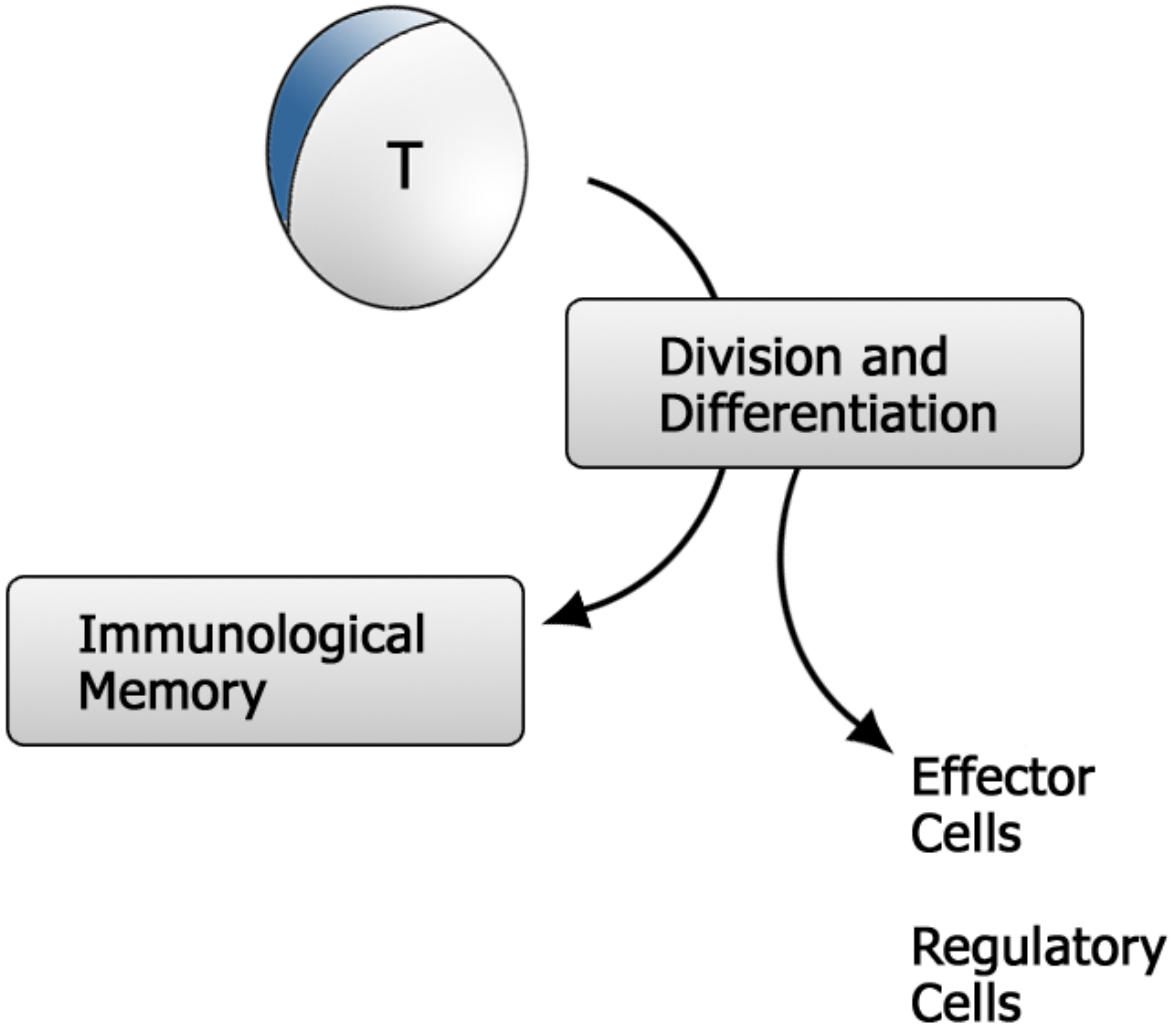
Two Main Types of Lymphocytes



Lymphocyte Maturation



Diversity of T Lymphocytes



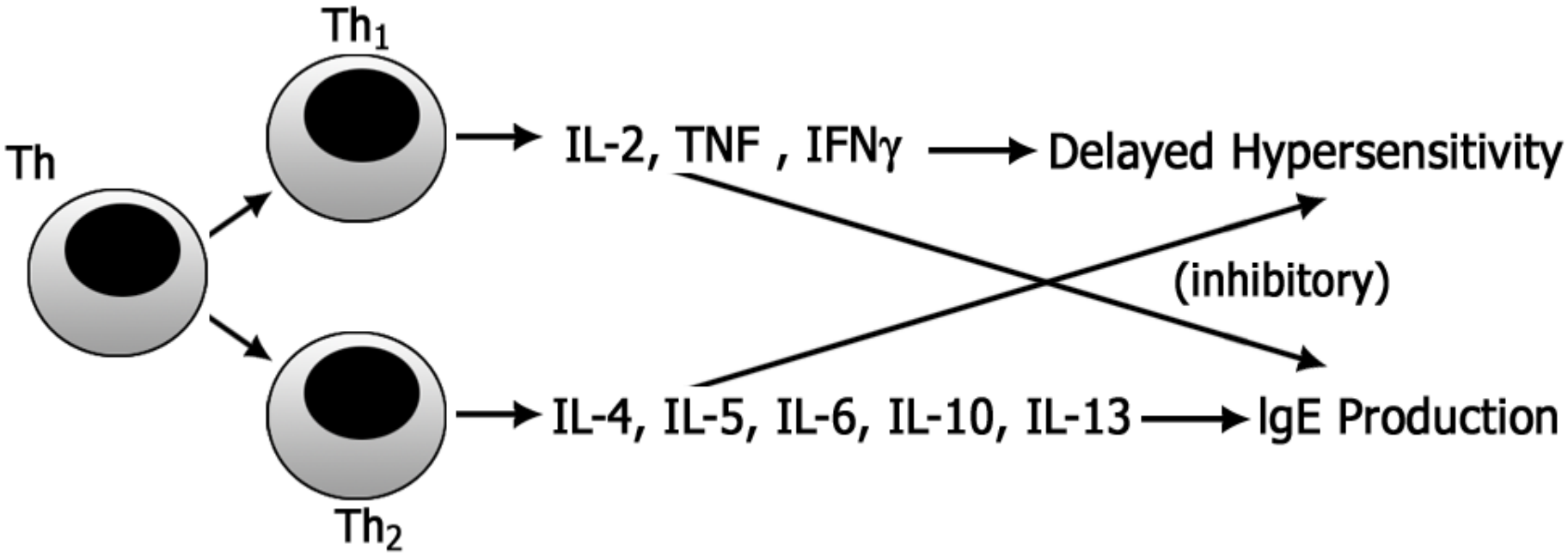
T Effector Cells

Cytotoxic T Lymphocytes

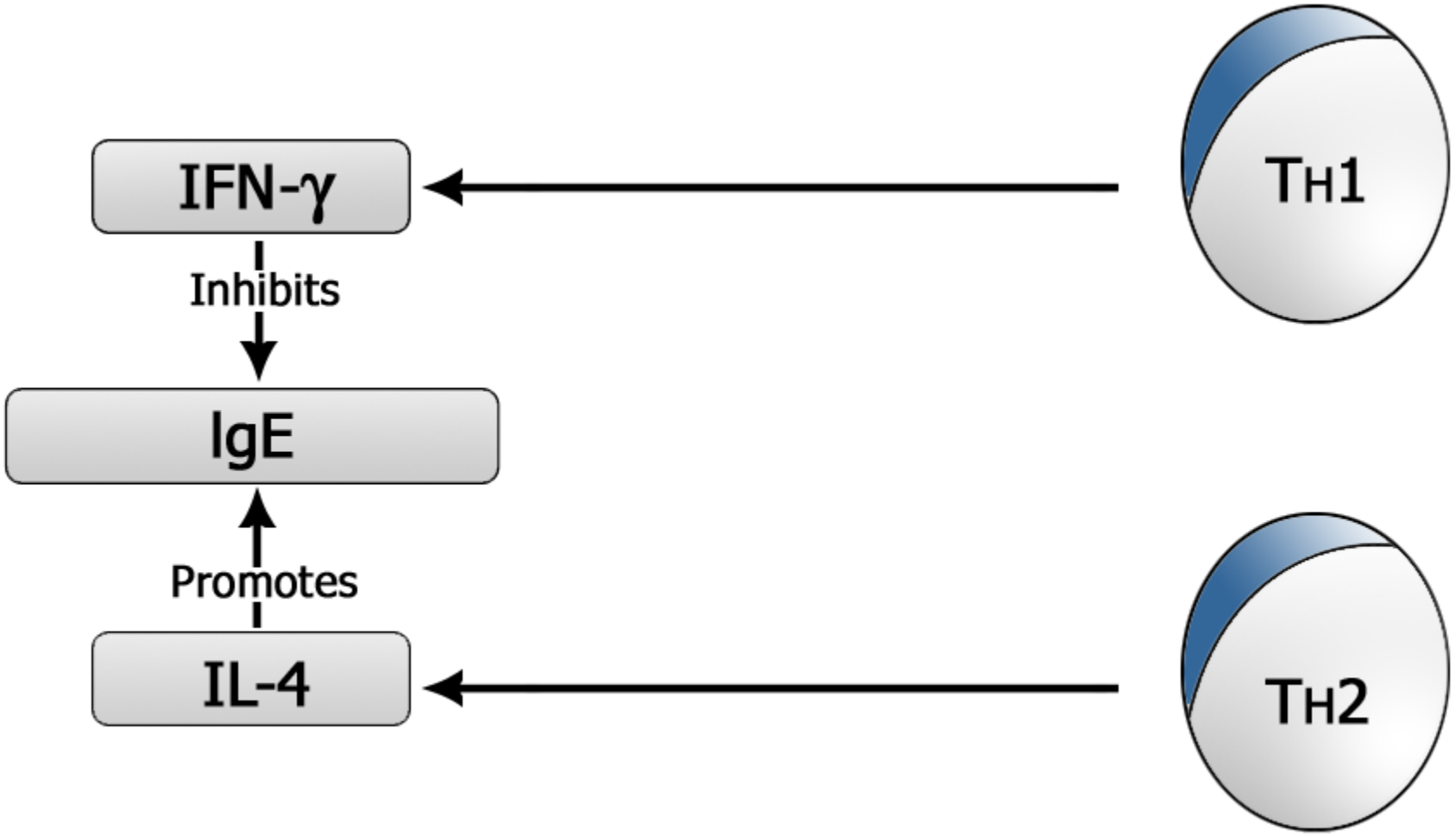
- Destruction of virus-infected host cells

Cytokine producing cells

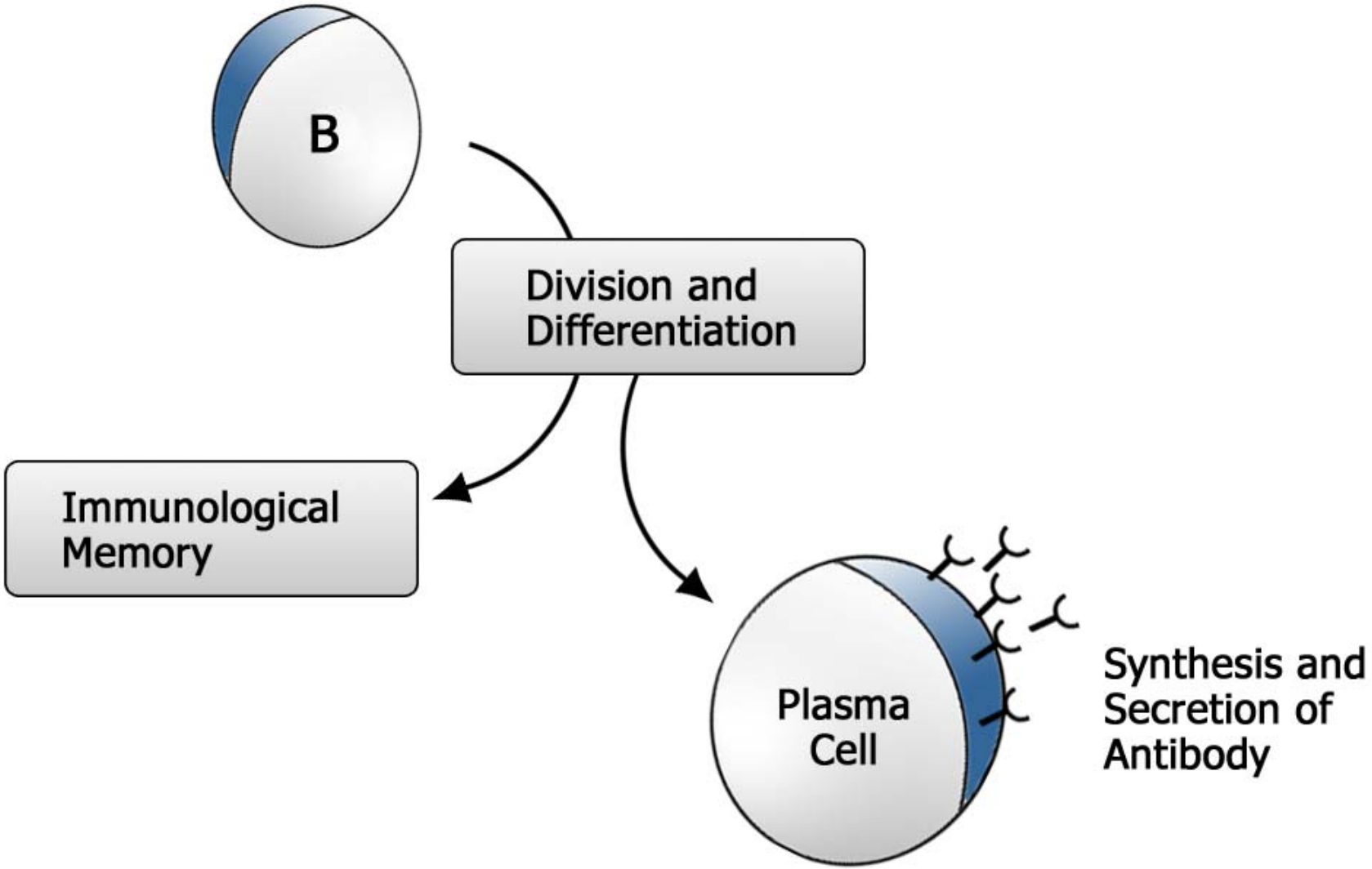
- Augmentation of macrophage function and other aspects of protective immunity


Th
Th1
Th2
IL-2, TNF , IFNγ
Delayed Hypersensitivity
(inhibitory)
IL-4, IL-5, IL-6, IL-10, IL-13
IgE Production

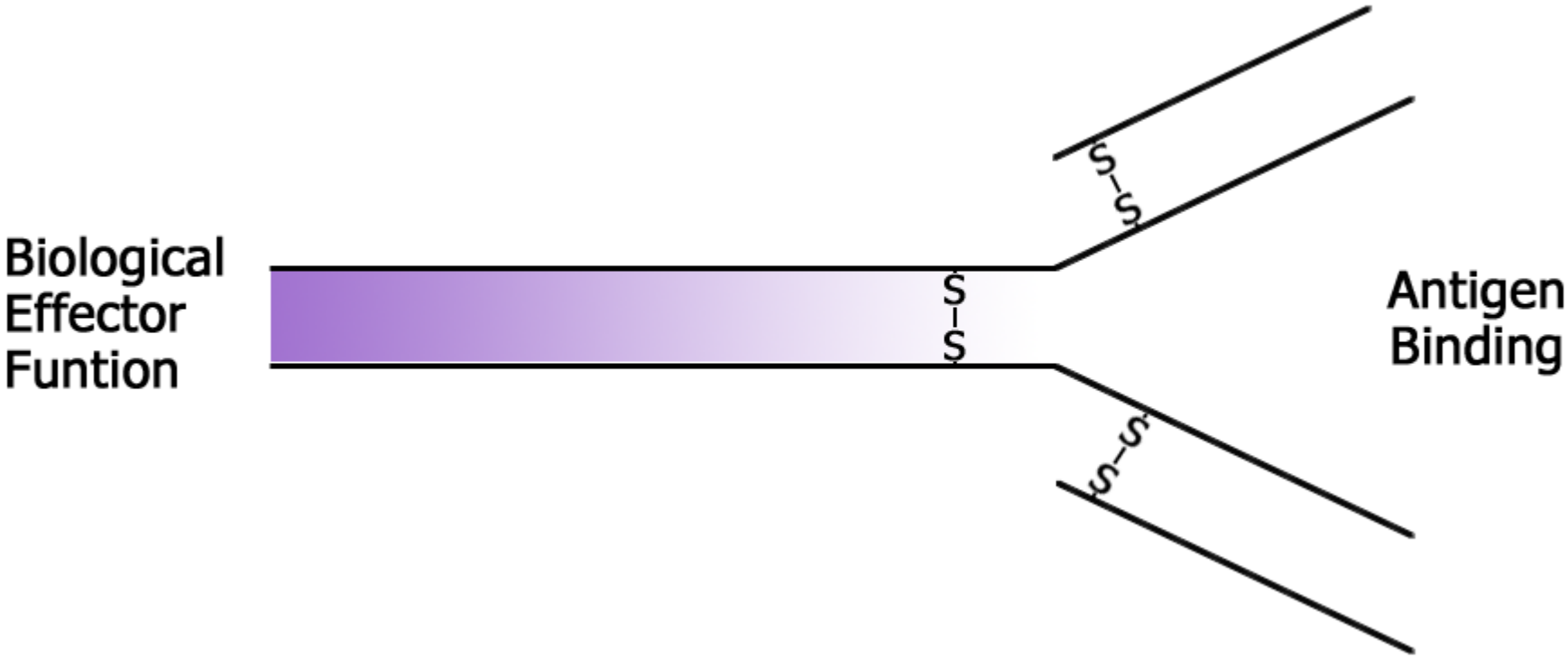
Cytokines Produced by the Two Main Classes of TH Cells Exert Reciprocal Antagonistic Effects on IgE Antibody Production



The End-Cell of B Lymphocyte Differentiation Is the Plasma Cell



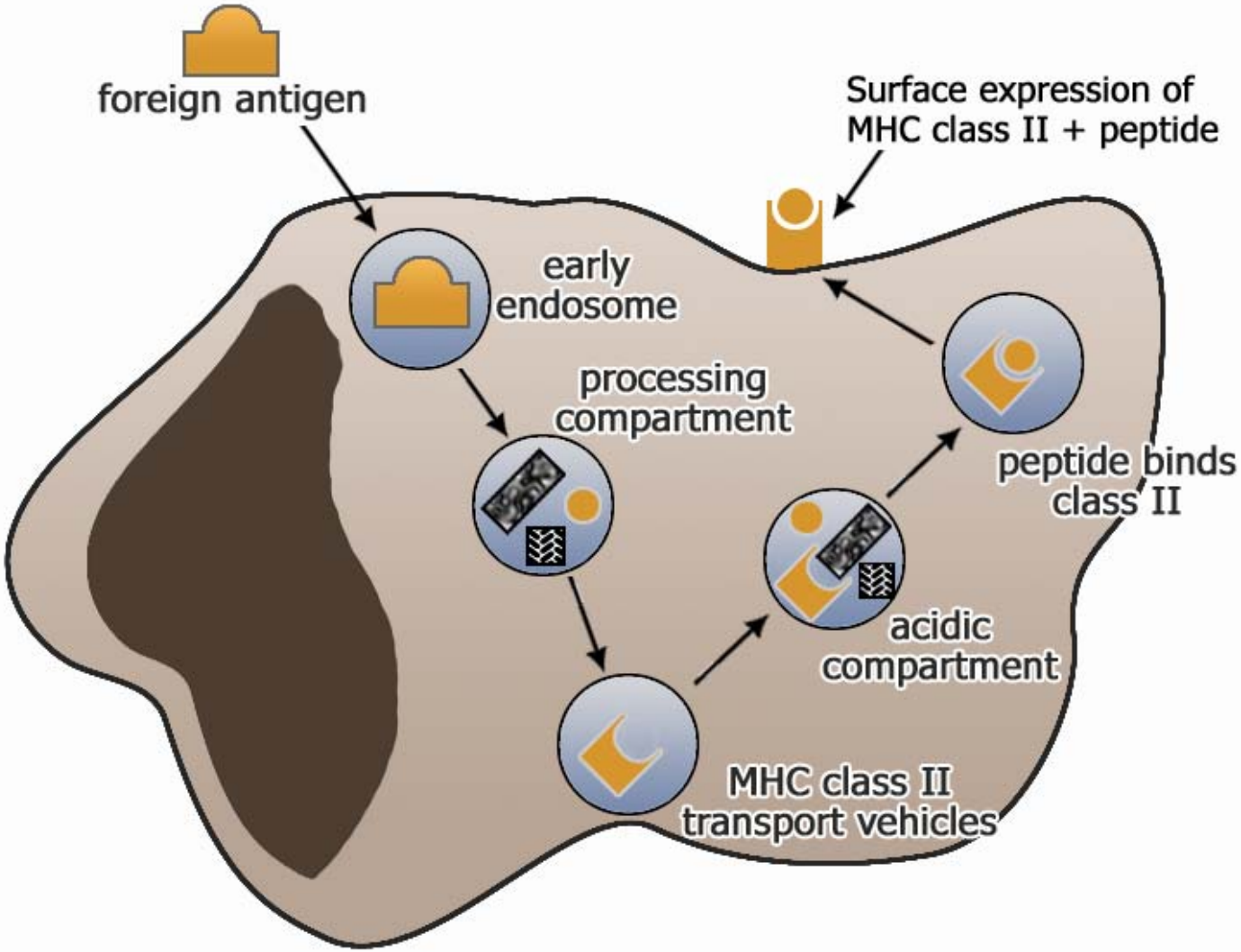
Antibody Structure



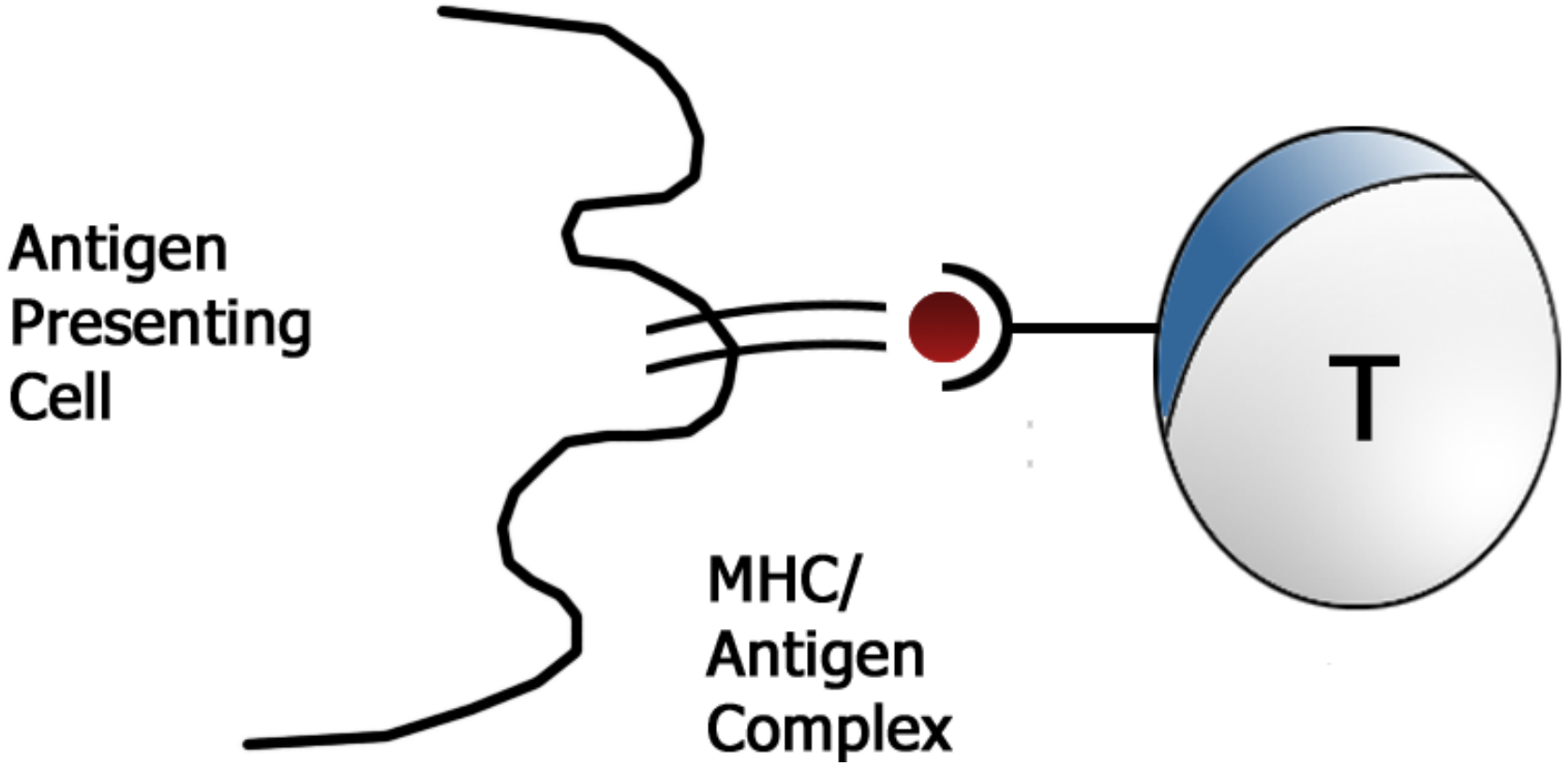
Functions of Antibodies

- Lysis with complement
- Opsonization for phagocytosis
- Neutralization of toxins
- Protection of mucosal surfaces
- Transplacental transfer

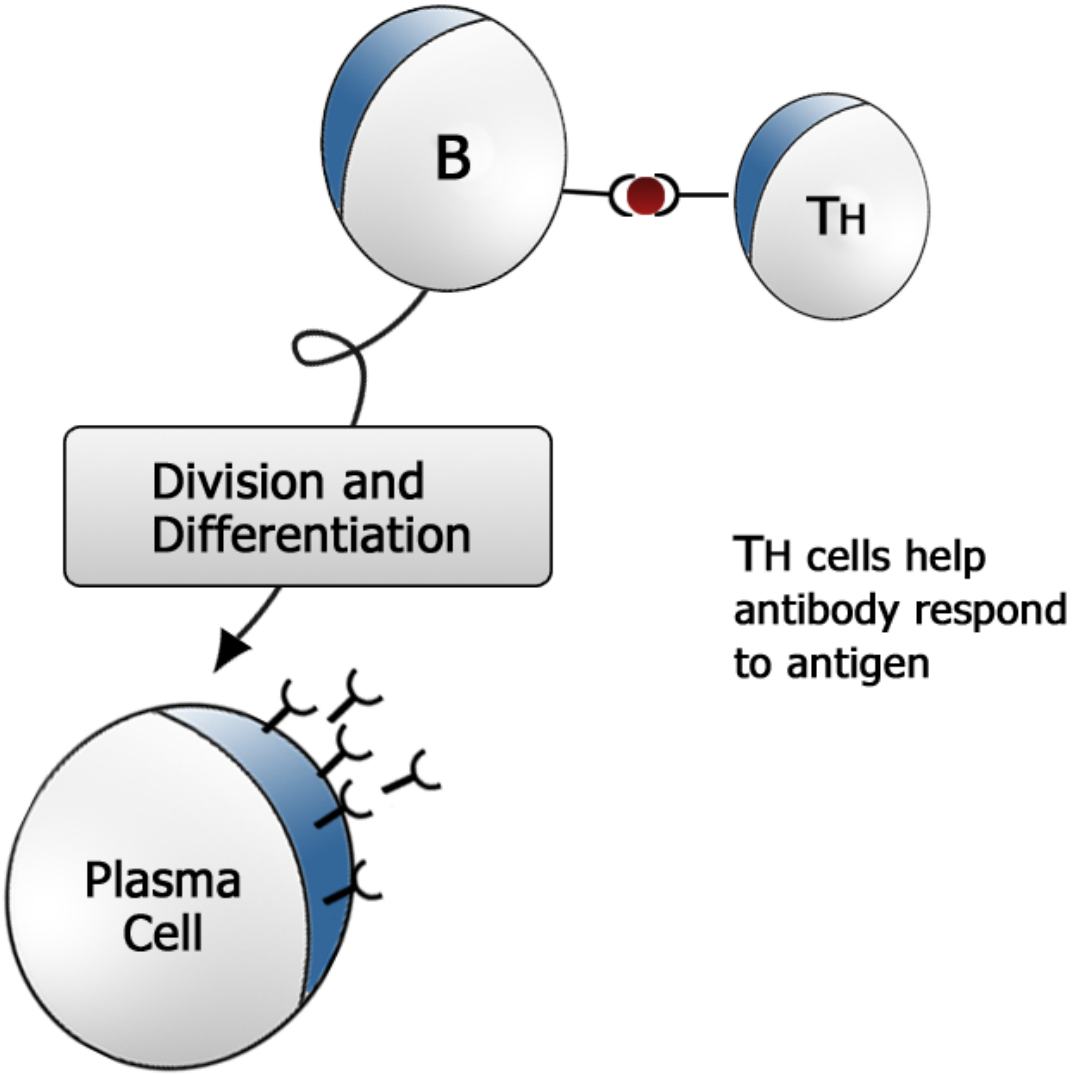
General Schematic of Antigen Processing and Presentation



T Lymphocytes Recognize Processed Antigen Presented with "Self" (Major Histocompatibility Complex) Molecules



TH Cells and the Regulation of IgE Antibody Production



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Section C

Immunologically Mediated Tissue Injury

Immunologically Mediated Tissue Injury

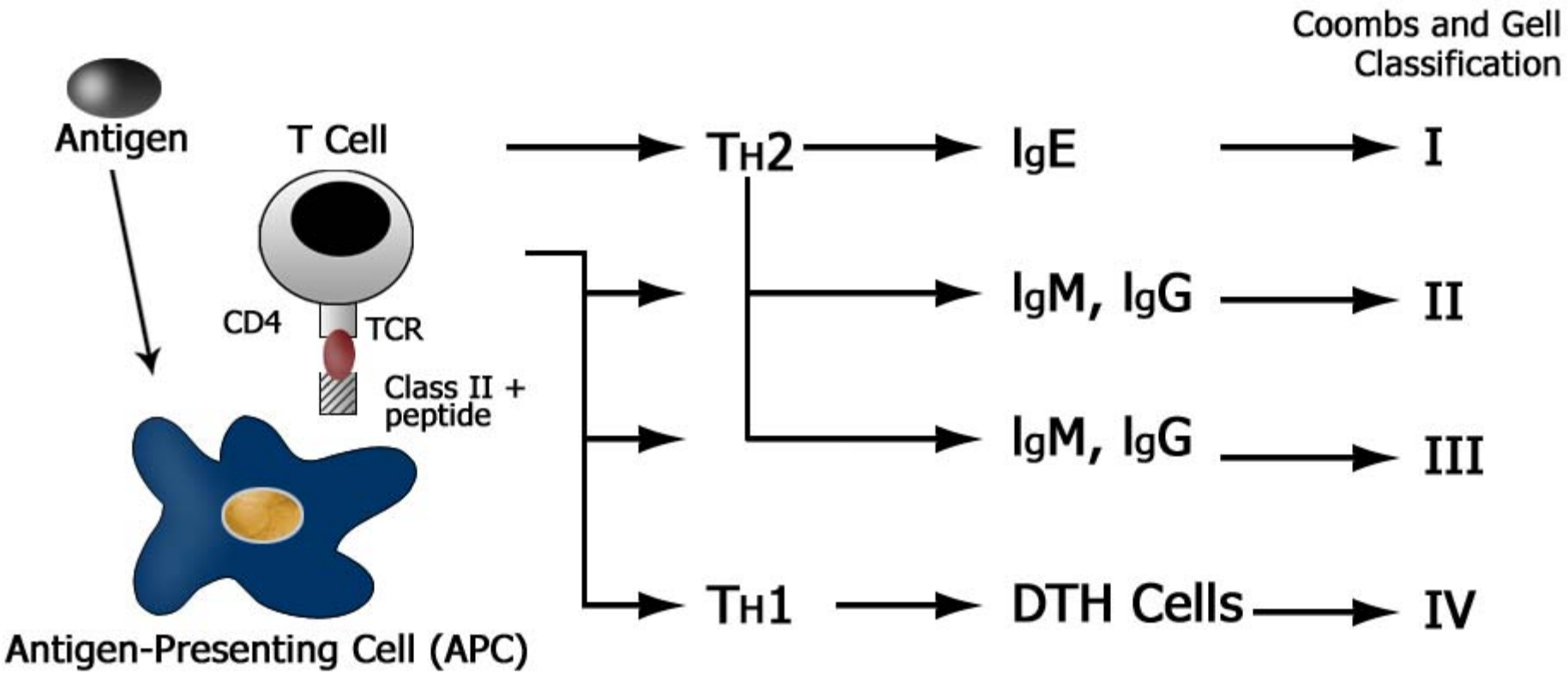
- While immune responses constitute a protective mechanism to foreign organisms, they can lead to tissue damage
- An immune response that results in tissue injury is broadly referred to as a hypersensitivity reaction
- Such responses are classified into four categories based on the immune mechanisms involved

Classification of Immunologic Diseases

- **Type I:** immediate hypersensitivity
  - IgE antibody; mast cells
- **Type II:** antibody-mediated
  - IgM, IgG antibodies against tissue or cell surface antigens

Classification of Immunologic Diseases

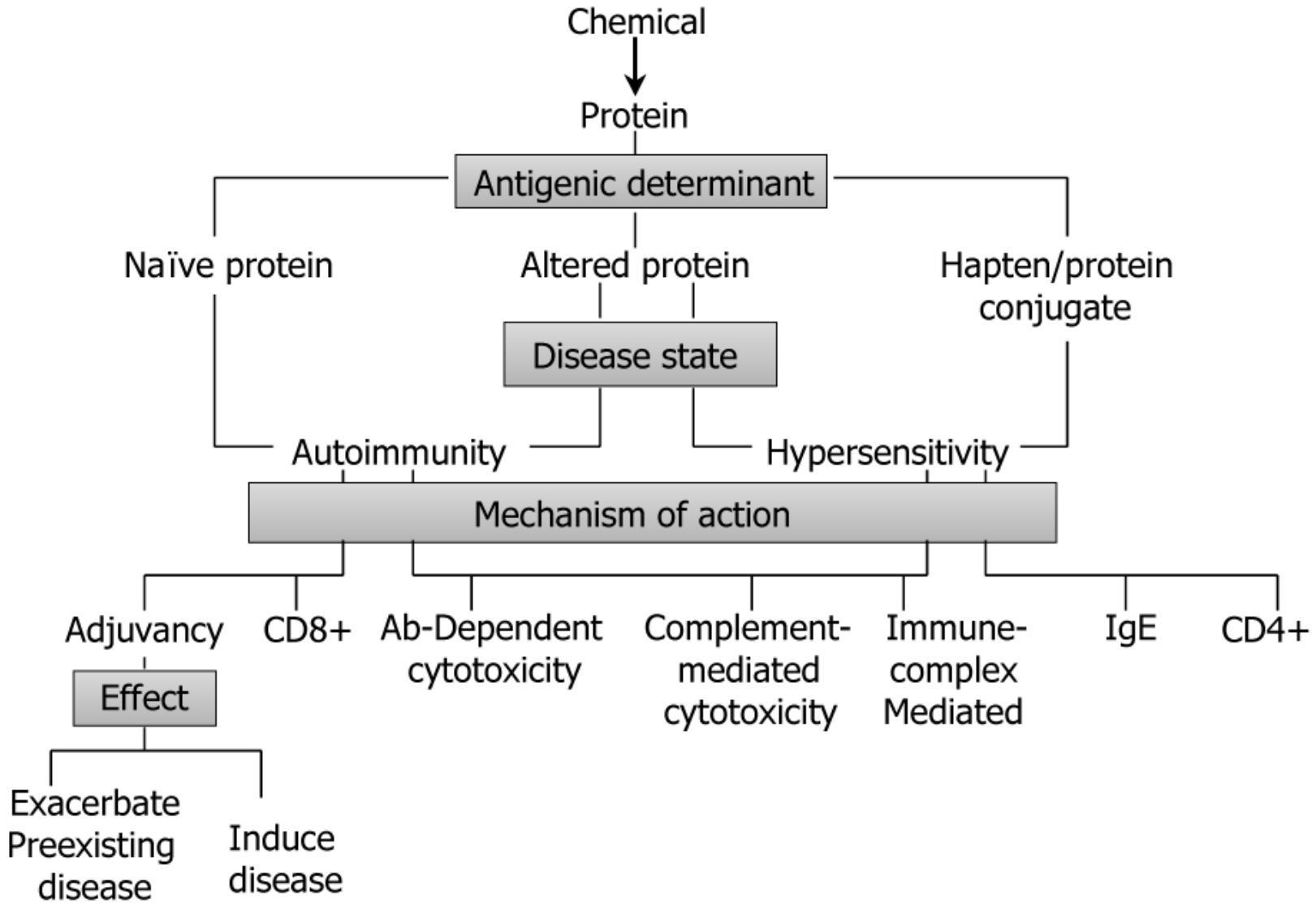
- **Type III:** immune complexes of IgG or IgM antibodies
- **Type IV:** delayed-type hypersensitivity
  - Sensitized CD4 lymphocytes, macrophages


Coombs and Gell Classification
Antigen
T Cell
CD4
TCR
Class II + peptide
Antigen-Presenting Cell (APC)
TH2
IgE
I
IgM, IgG
II
IgM, IgG
III
TH1
DTH Cells
IV

Hapten

- A **hapten** is a substance that is too small to induce an immune response (i.e., low-molecular-weight chemicals)
- Haptens can induce an immune response when they bind to a larger carrier molecule (i.e., protein) to form a hapten-carrier conjugate (adduct)

Schematic Diagram of Chemical Interaction Leading to Hypersensitivity Reactions or Autoimmunity

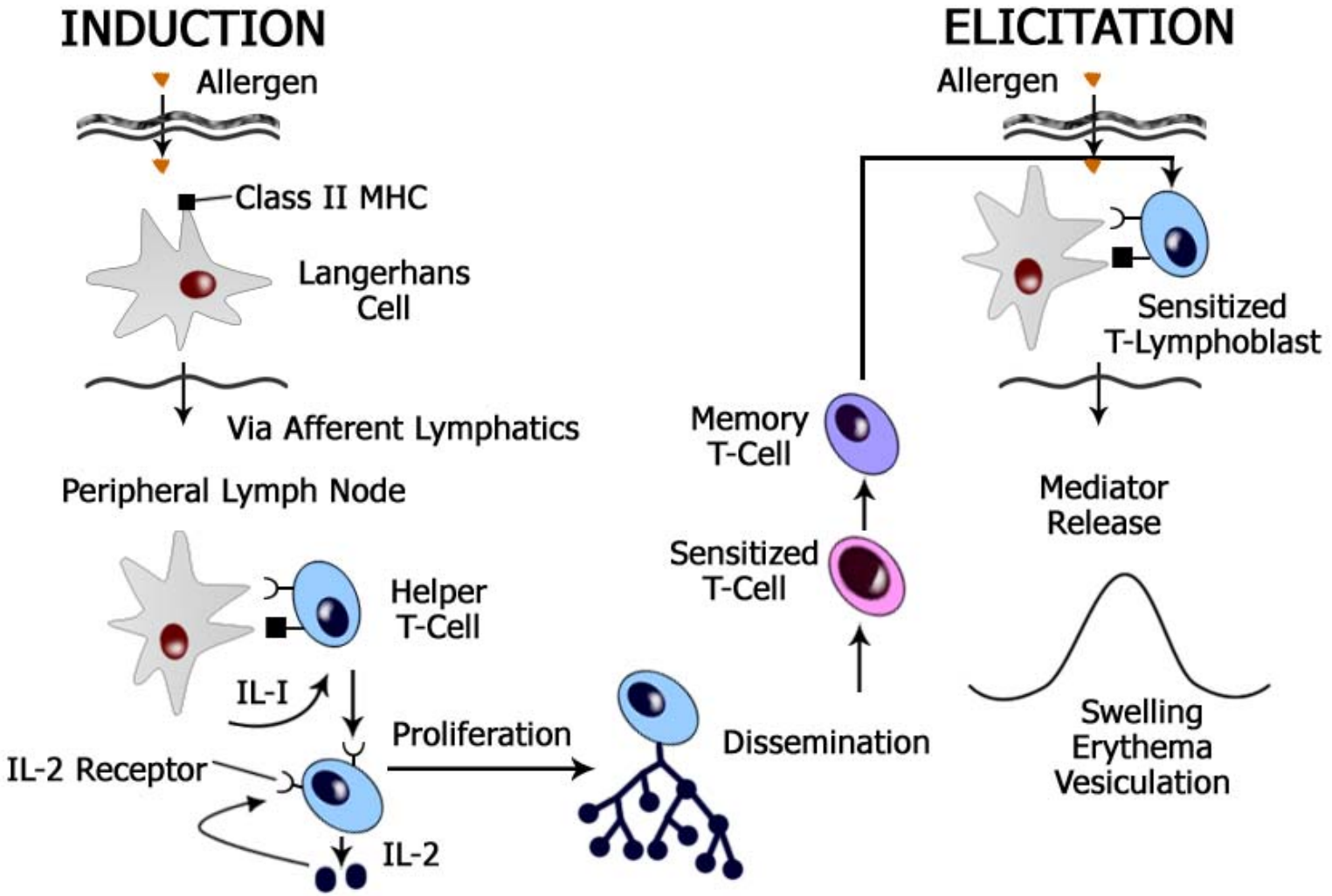


Allergic(Hypersensitivity) Reactions Take Place in Two Stages

First encounter with antigen → **Sensitization phase**

Second or subsequent encounter with antigen → **Elicitation phase**

Immunologic Mechanism of Contact Sensitization (Skin)



Development of Allergic Contact Dermatits, a Delayed Hypersensitivity Reaction

Poison ivy
catechol molecules

Skin protein

Catechols combined
with skin proteins

7-10 days

1-2 days

Primary contact

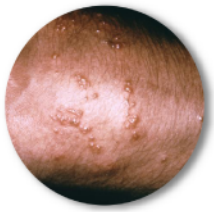
T-cells → T memory cells

↓

No dermatitis

Secondary contact

T memory cells → Many active cells



↓

Dermatitis

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Contact Dermatitis

Contact dermatitis around a healing rug burn.

Question

- The skin and lungs are often target organs of toxicity by immune-mediated mechanisms — **Why?**

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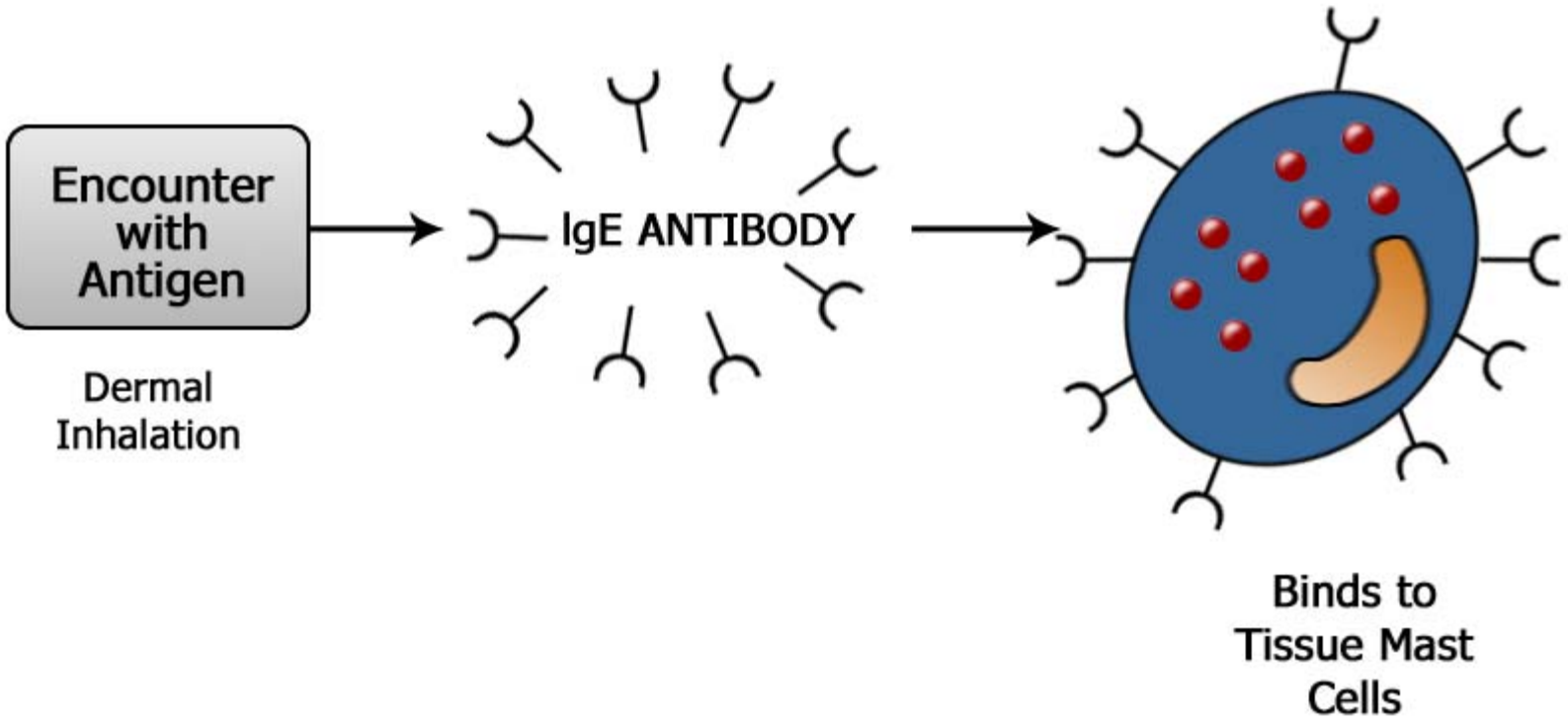
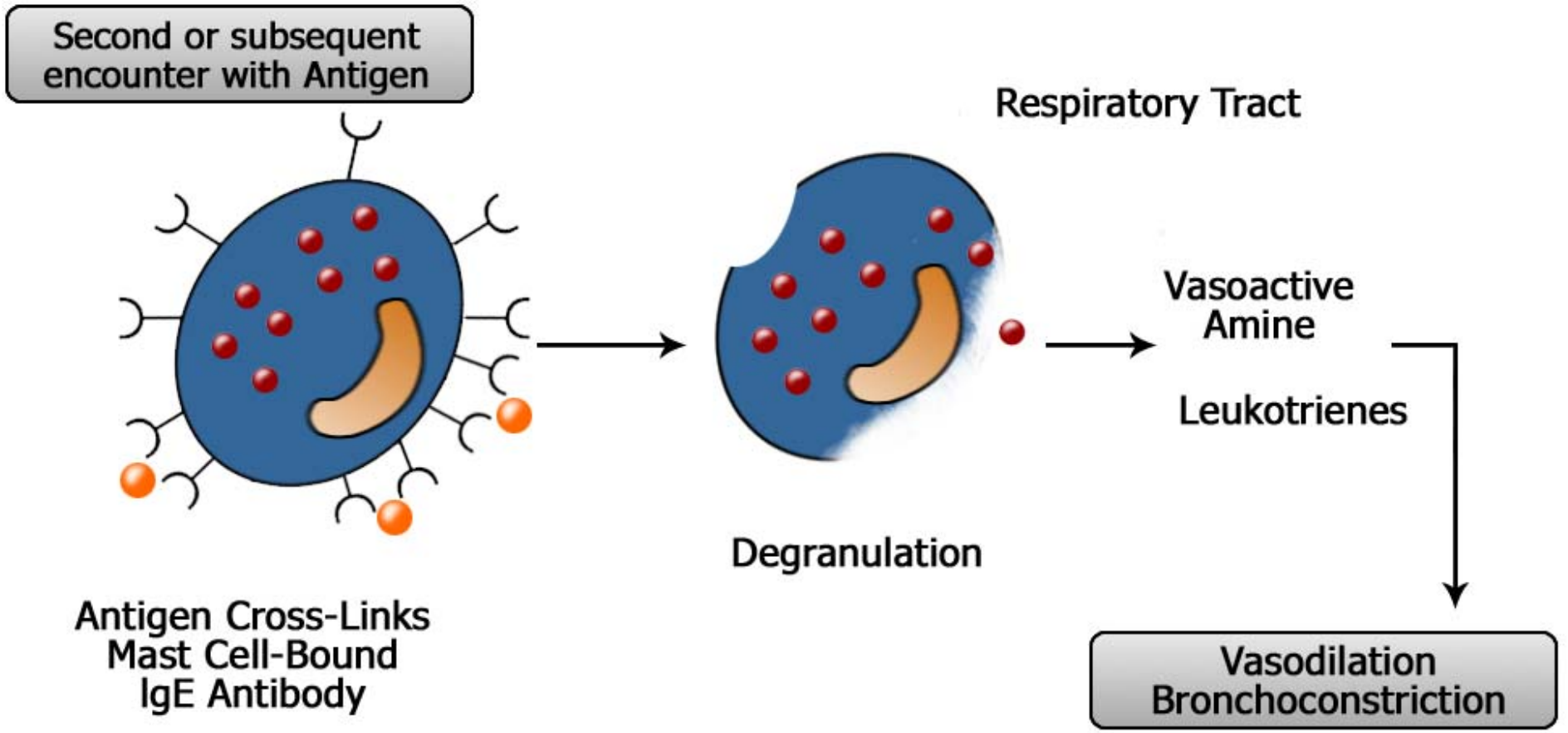
Section D

Case Studies: TMA and Beryllium

Respiratory Allergy Sensitization Phase



Respiratory Allergy Elicitation Phase



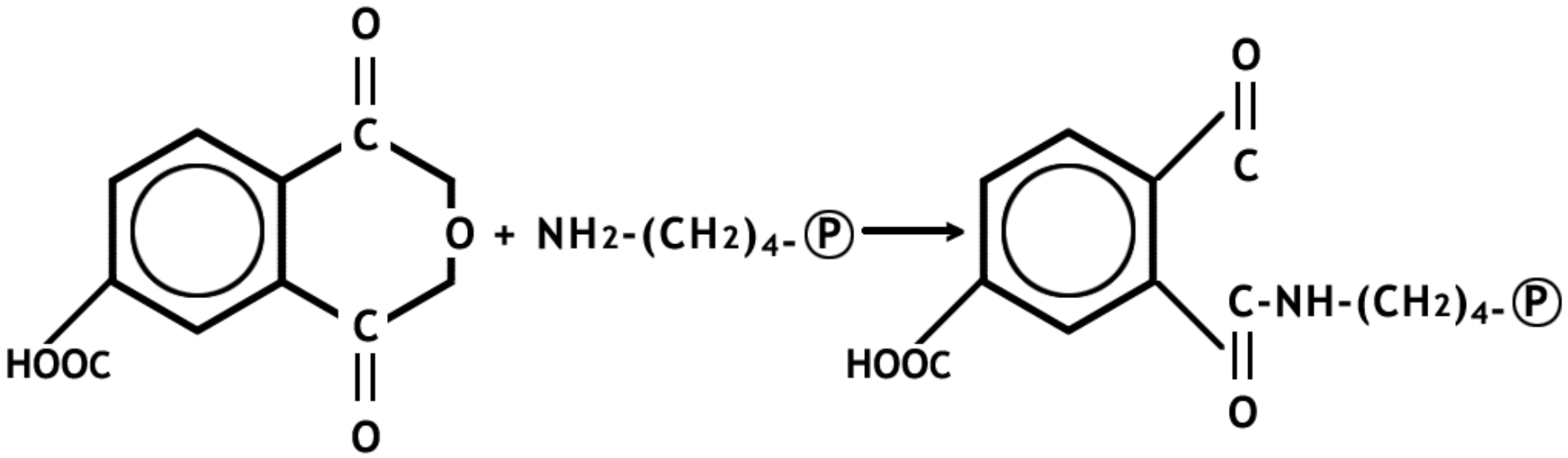
Trimellitic Anhydride

Elicits Immediate Hypersensitivity in Lung

- TMA covalently reacts with protein to form immunogenic hapten-protein conjugates which can elicit the formation of IgE antibody as detected by RAST
- (Radioallergosorbent TesT) measures IgE antibody in serum with a radioactive indicator system

Immunogenic Hapten–Protein Conjugates

- Example of how a chemical covalently reacts with protein to form immunogenic hapten–protein conjugates



Average Airborne TMA Dust Concentrations

As Measured for Several Different Jobs

Airborne TMA Dust* (mg/m3)

Job	1974-78	1979	1980	1981	1982	1983	1984
Station Operator	2.1	0.0006	0.01	0.01	0.03	<0.001 (12/82)	<0.04
Ass't Operator	0.82	0.0002	0.01	0.01	0.02	0.10	<0.04
Packager	0.007	0.0007 0.08	0.11	0.10	0.18	0.05	0.32

*Average TMA dust concentration of 5 years

Annual Determinations of Total Antibody and Specific IgE Bound to ^{123}I-TM-HAS from 1979–1983

	Total Antibody (ng/ml ^{123}I-TM-HAS Bound)				
	1979	**1980**	**1981**	**1982**	**1983**
Group 1 Worker					
1	100,000	ND	18,000	9,600	2,400
2	12,500	2,400	0	0	0
3	9,500	6,600	4,600	2,800	340
4	2,200	3,100	1,050	Trace	600

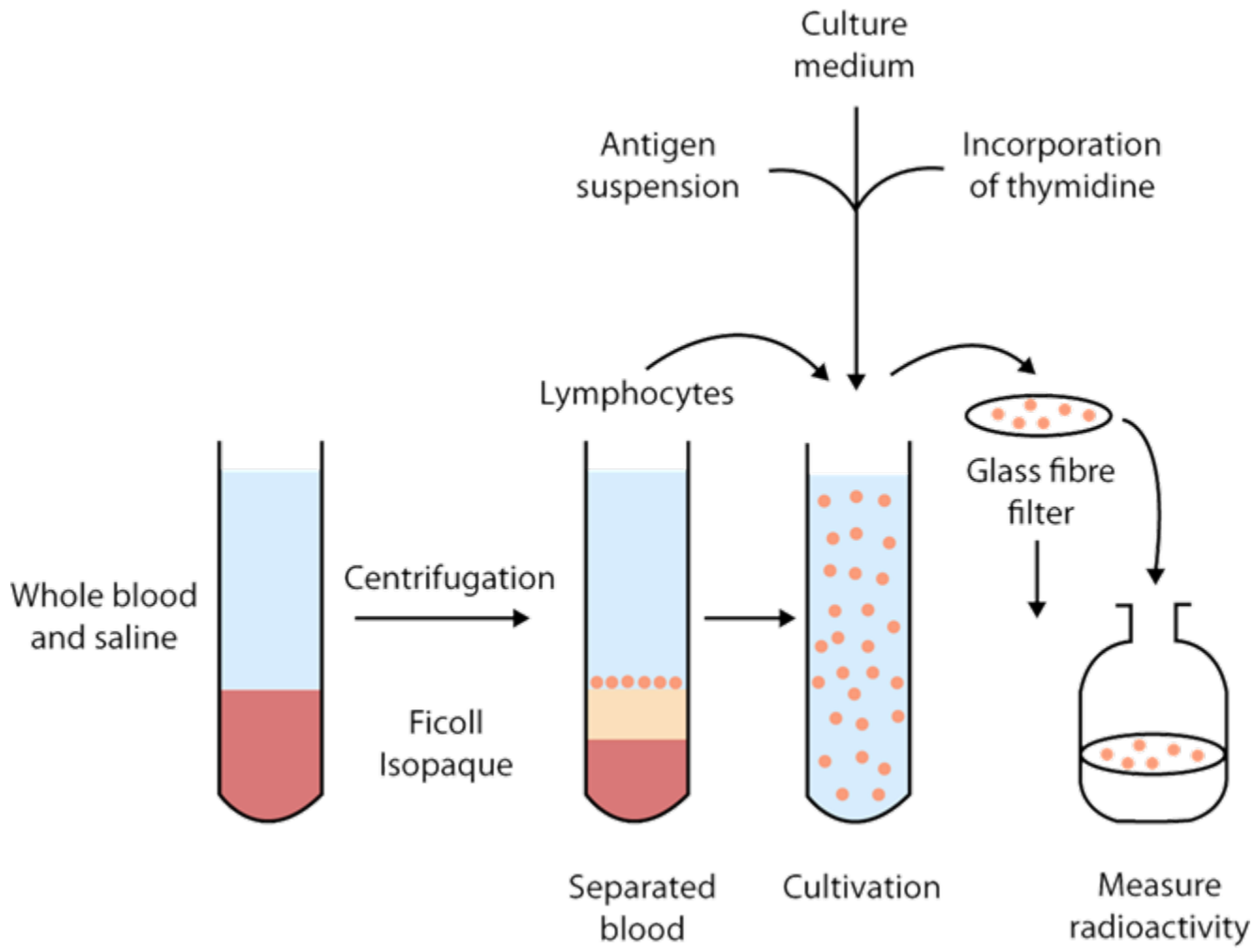
Worker	TMA Exposure	TMA-Induced Symptoms	Total Antibody *(ng/ml ^{123}I-TM-HSA Bound)*	Specific IgE *(ng/ml ^{123}I-TM-HSA Bound)*
1	Assistant operator	LRSS	100,000	0
2	Operator	LRSS	12,500	0
3	Assistant operator	LRSS	9,500	0
4	Maintenance operator	Rhinitis	0	1.1
5	Laboratory technician	Rhinitis/ asthma	0	5.2
6	Extruder operator	None	2,200	0.23
7–20	—	Irritant or none	0	< 1.0

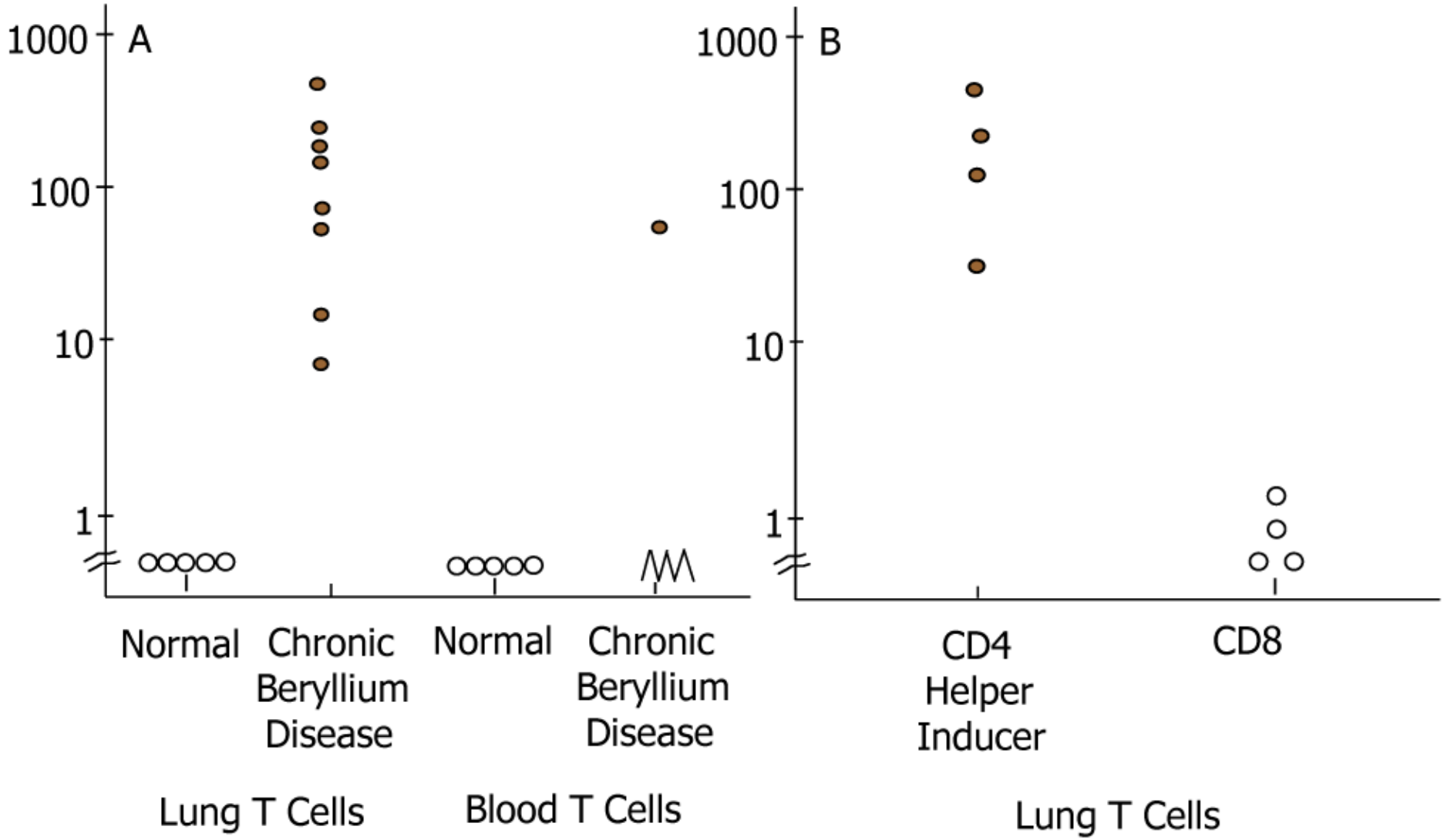
Initial clinical evaluations and total antibody and specific IgE binding to ^{125}I-TM-HAS of 20 workers—group 1

Beryllium Induces Delayed Type Hypersensitivity in Lung

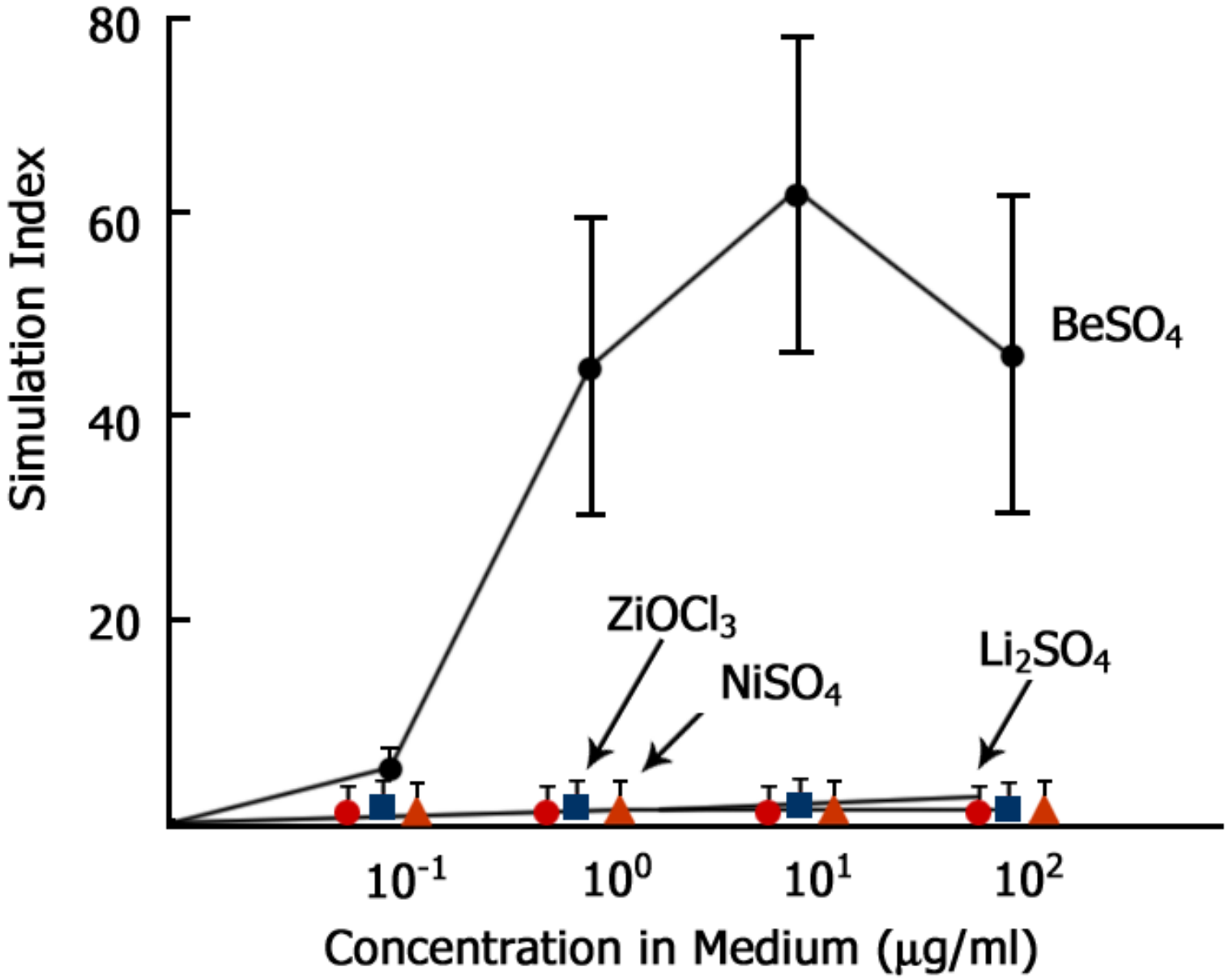
- Following inhalation exposure, beryllium can have a half-life from several weeks to 6 months in the lungs
- In the lungs, beryllium can act as a direct irritant leading to non-specific inflammation
- In susceptible individuals (3–6%), beryllium exposure results in a DTH response

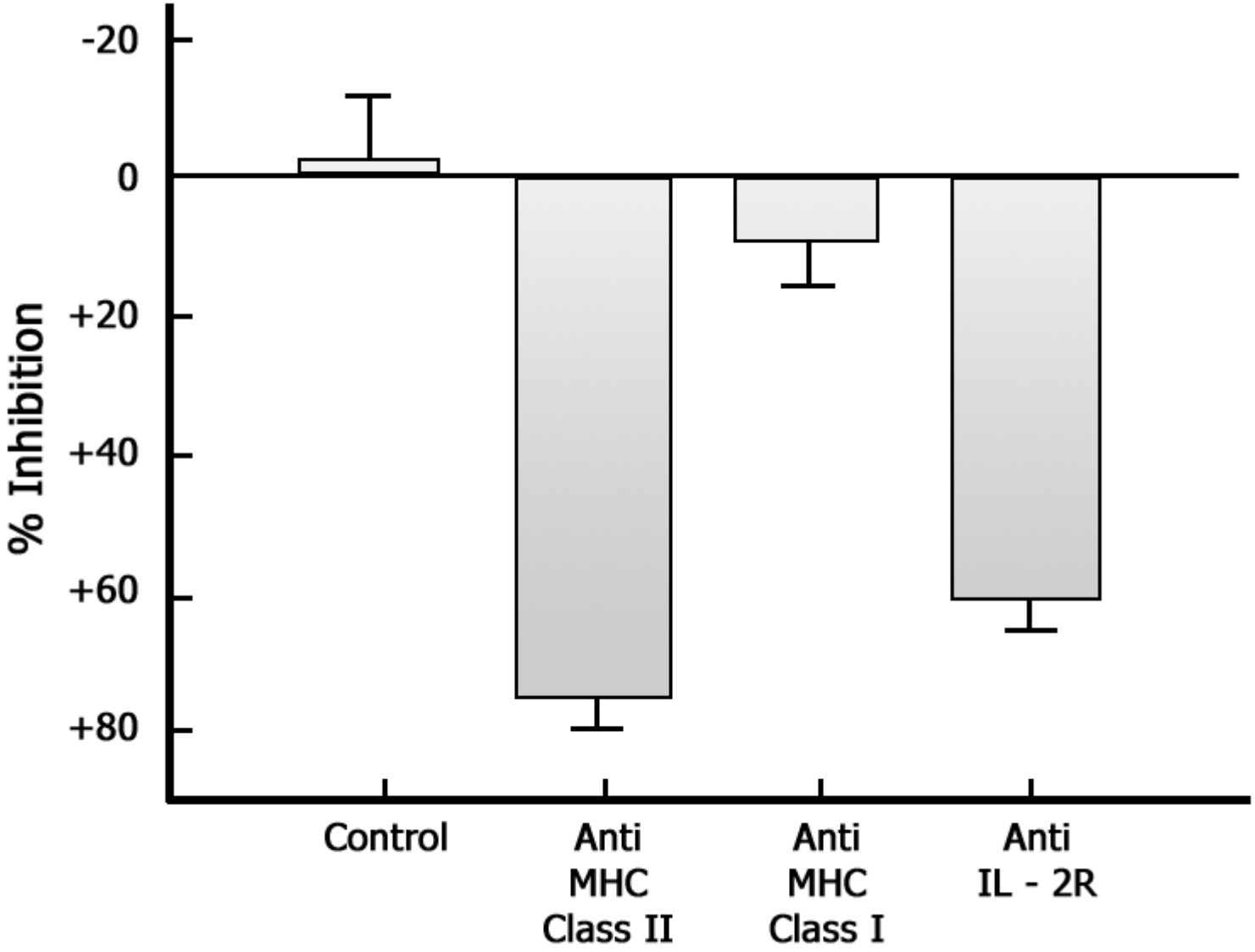
Lymphocyte Stimulation Test





In vitro proliferation of purified T-cells (A) and T-cell subpopulations (B) from the lungs and blood of patients with chronic beryllium disease and controls in response to beryllium


80
60
40
20
Simulation Index
BeSO4
ZiOCl3
NiSO4
Li2SO4
10-1
100
101
102
Concentration in Medium (µg/ml)


-20
0
+20
+40
+60
+80
% Inhibition
Control
Anti MHC Class II
Anti MHC Class I
Anti IL - 2R