Type IV Hypersensitivity Reactions

- First observed by Robert Koch in 1890 when he injected a filtrate from *M. tuberculosis* cultures into animals .This response was called the =Delayed Type Hypersensitivity reaction
- Main features of a Type IV reaction:
- Delay in time for reaction to develop
- Recruitment of macrophages

Type 4 – Cell mediated hypersensitivity

-T cells involved (td) – delayed hypersensitivity – symptoms are slow, at least a day or two due to

1. Time is required for the T cells and macrophages to migrate to site of foreign antigens .

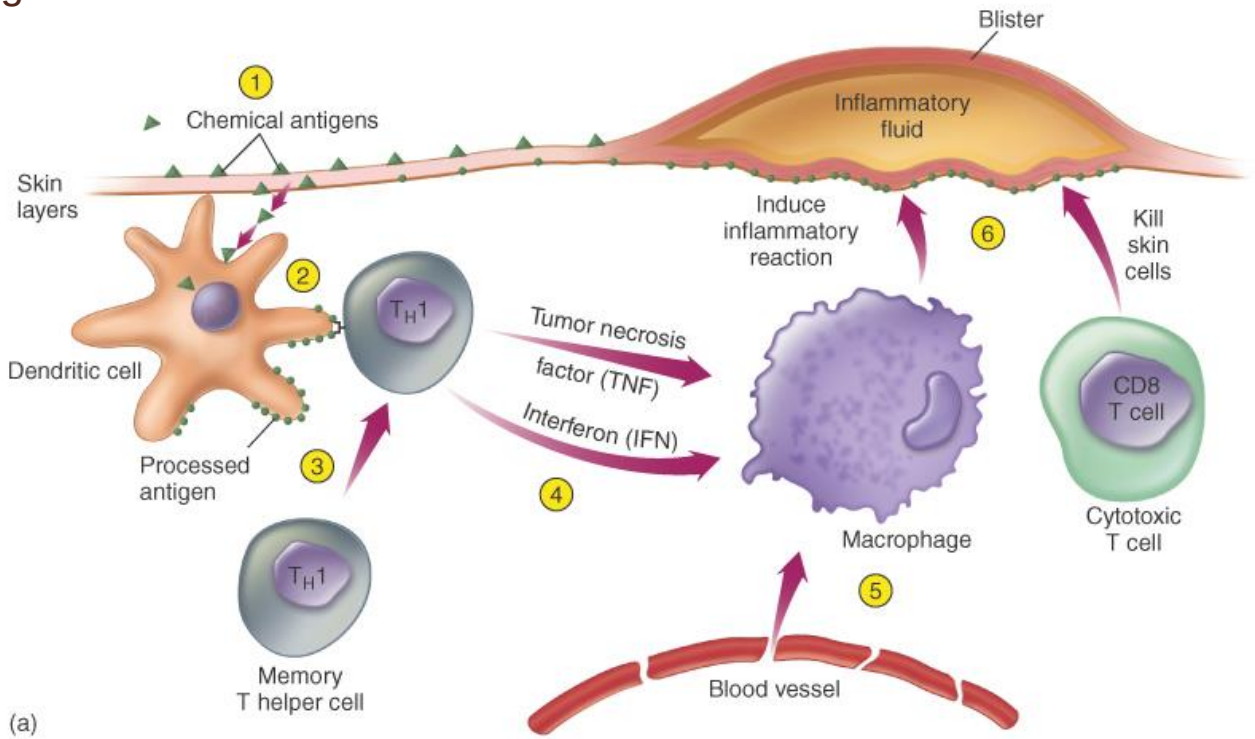
2. Allergic contact dermatitis is an example (poison ivy) .

3. T cells are exposed to allergen, develop clone of T memory cells, these are circulating and are ready to interact with later exposure to antigen .

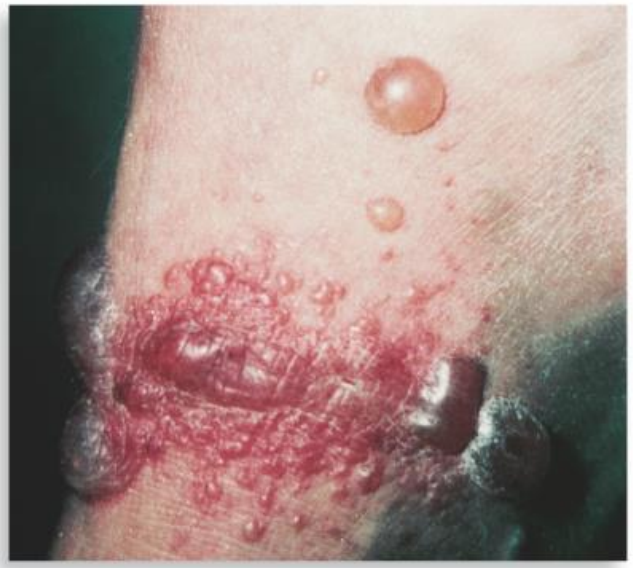
4. TB skin test uses this type of reaction to detect earlier exposure to TB disease .

5. Inflammation reaction – macrophages dump (degranulate), (histamine reaction in tissue) redness, swelling, itch

Fig. 16.15



1. Lipid-soluble chemicals are absorbed by the skin.
2. Dendritic cells close to the epithelium pick up the allergen, process it, and display it on MHC receptors.
3. Previously sensitized T_H1 (CD4) cells recognize the presented allergen.
4. Sensitized T_H1 cells are activated to secrete cytokines (IFN, TNF) that
5. attract macrophages and cytotoxic T cells to the site.
6. Macrophage releases mediators that stimulate a strong, local inflammatory reaction. Cytotoxic T cells directly kill cells and damage the skin. Fluid-filled blisters result.



(b)

TABLE 15-6 Intracellular pathogens and contact antigens that induce delayed-type (type IV) hypersensitivity

Intracellular bacteria
- *Mycobacterium tuberculosis*
- virus
- *Mycobacterium leprae*
- *Listeria monocytogenes*
- *Brucella abortus*

Intracellular fungi
- *Pneumocystis carinii*
- *Candida albicans*
- *Histoplasma capsulatum*
- *Cryptococcus neoformans*

Intracellular parasites
- *Leishmania* sp.

Intracellular viruses
- Herpes simplex
- Variola (smallpox)
- Measles virus

Contact antigens
- Picrylchloride
- Hair dyes
- Nickel salts
- Poison ivy
- Poison oak

Table 15-6
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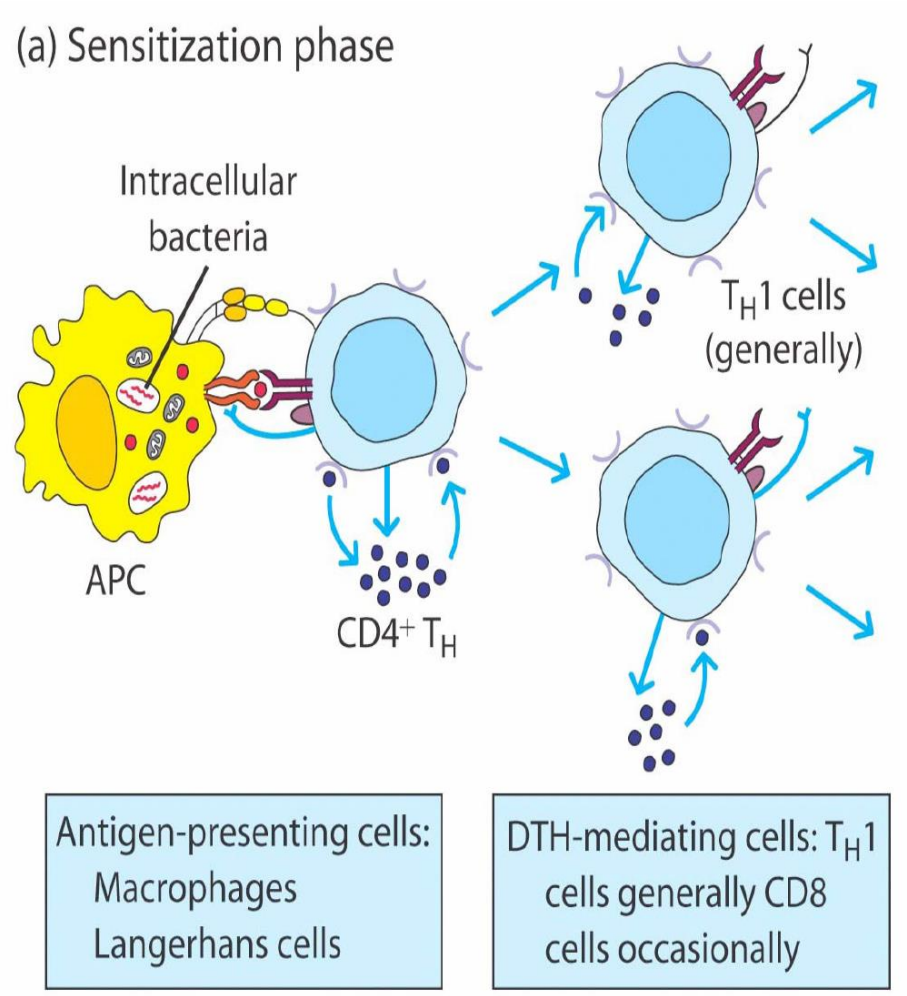
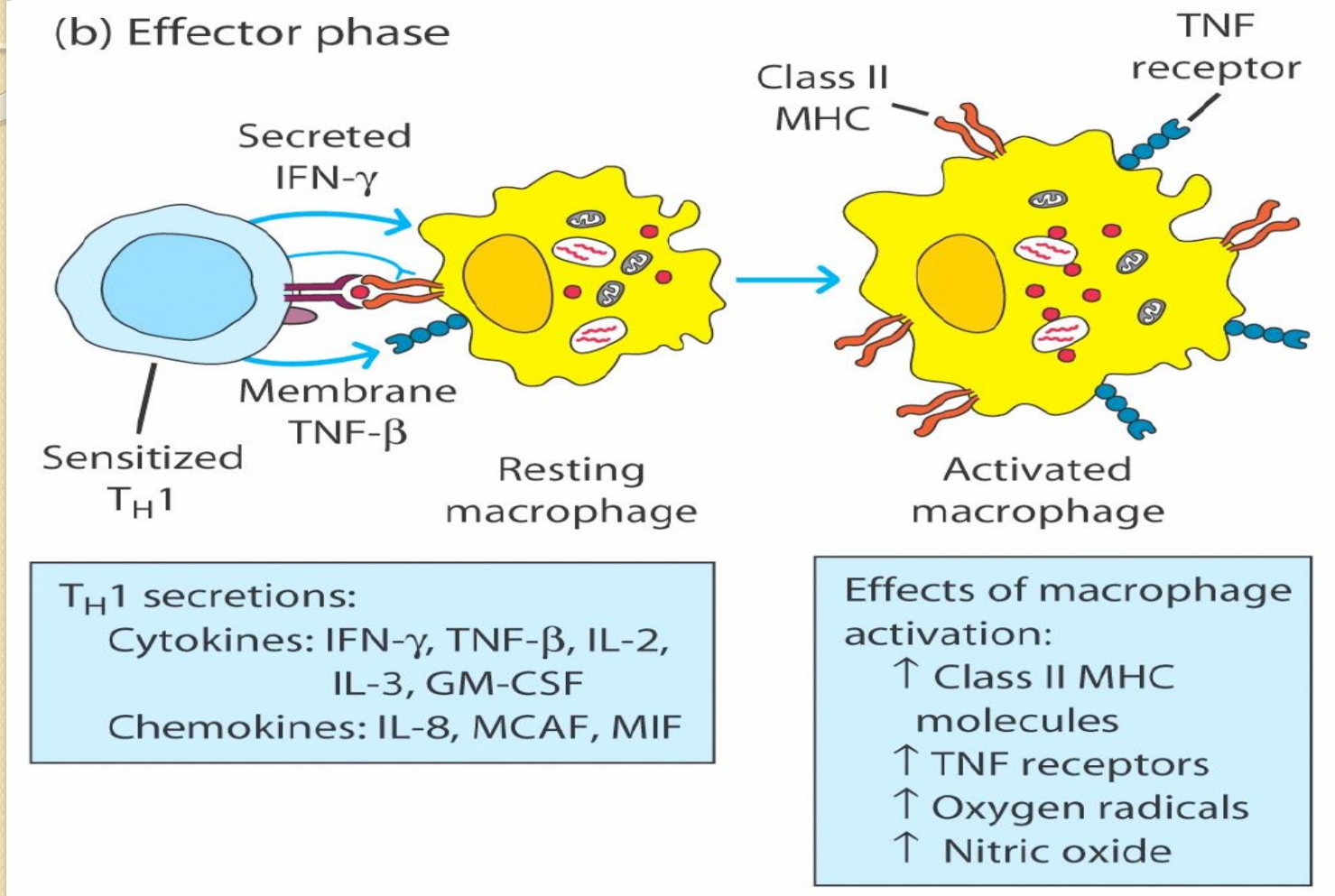
Sensitization phase

- the time following antigen encounter that is required for TH1 cell activation by APCs
- Usually 1-2 weeks


(a) Sensitization phase
Intracellular bacteria
APC
CD4+ TH
TH1 cells (generally)
Antigen-presenting cells:
Macrophages
Langerhans cells
DTH-mediating cells: TH1 cells generally CD8 cells occasionally

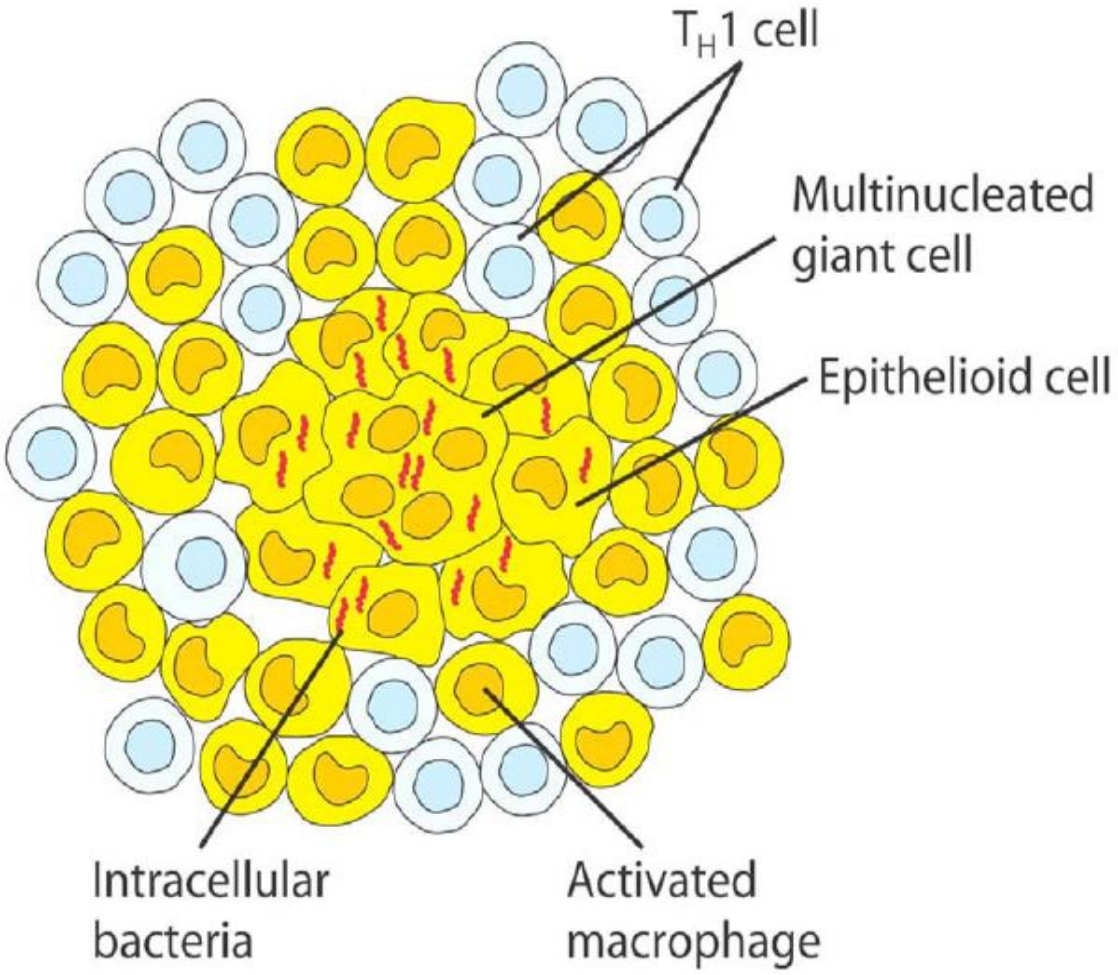
Effector phase

- Occurs on subsequent exposure to antigen
- Symptoms are usually apparent within 24 hours and peak between 48 and 72 hours.


(b) Effector phase
Secreted
IFN-γ
Membrane
TNF-β
Sensitized
T_H1
Resting
macrophage
Class II
MHC
TNF
receptor
Activated
macrophage
T_H1 secretions:
Cytokines: IFN-γ, TNF-β, IL-2,
IL-3, GM-CSF
Chemokines: IL-8, MCAF, MIF
Effects of macrophage
activation:
↑ Class II MHC
molecules
↑ TNF receptors
↑ Oxygen radicals
↑ Nitric oxide

Granulomatous Reaction

- Accumulated macrophage and lymphocytes develop into a granuloma


T_H1 cell
Multinucleated giant cell
Epithelioid cell
Intracellular bacteria
Activated macrophage

Contact Dermatitis

A Type IV reaction caused by contact with various molecules that can complex with Contact Dermatitis proteins .Eventually internalized by dendritic cells in the skin . leading to activation of a TH1 response .Poison oak, poison ivy, hair dyes, cosmetics, latex, turpentine, etc

Poison oak

Poison sumac

Poison ivy

- Contact dermatitis
- caused by poison oak

Development of delayed-type hypersensitivity reaction after a second exposure to poison oak. Cytokines such as IFN-, macrophage-chemotactic factor (MCF), and migration-inhibition factor (MIF) released from sensitized TH1 cells mediate this reaction. Tissue damage results from lytic enzymes released from activated macrophages.

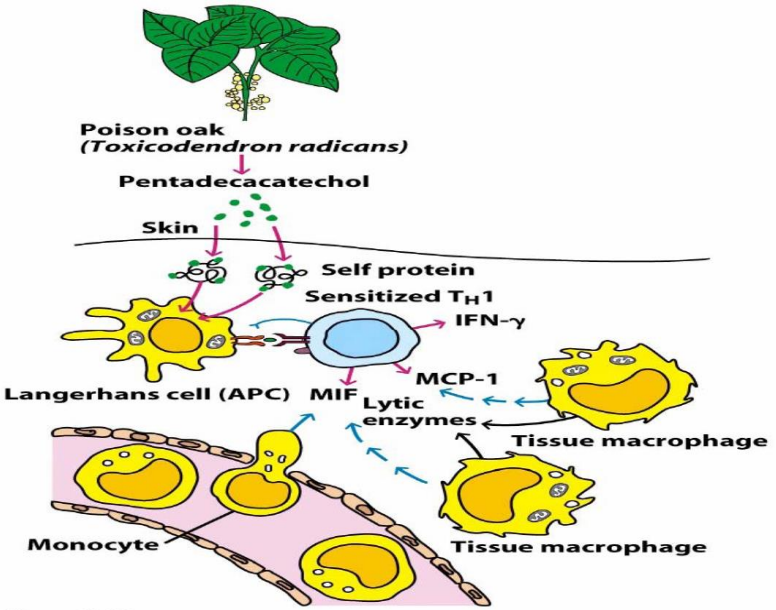


Figure 15-20
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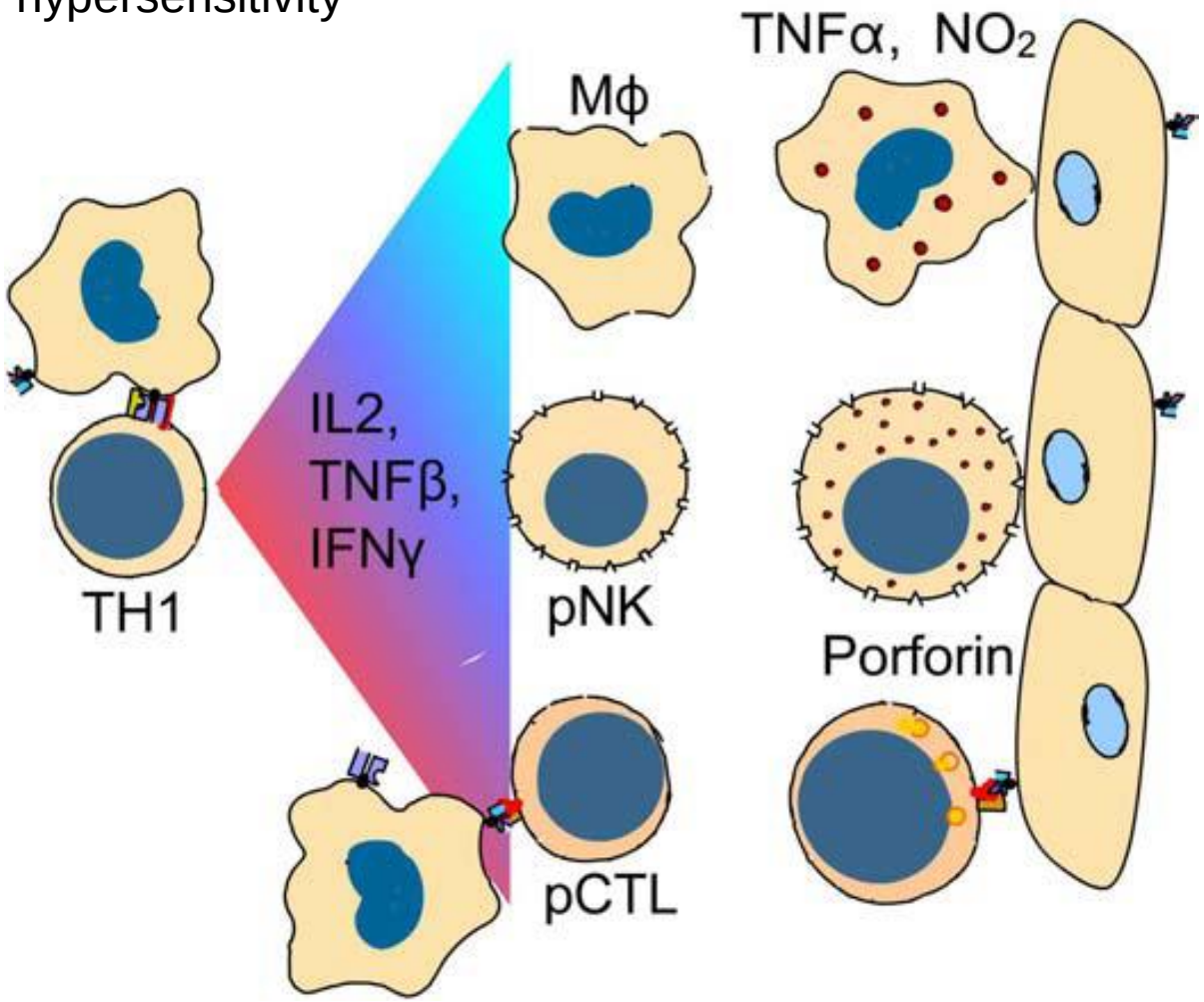
Mechanisms of damage in delayed hypersensitivity



- Mechanisms of damage in delayed hypersensitivity include T lymphocytes and monocytes and/or macrophages.
- Cytotoxic T cells (Tc) cause direct damage whereas helper T (TH1) cells secrete cytokines which activate cytotoxic T_ cells and recruit and activate monocytes and macrophages, which cause the bulk of the damage The delayed hypersensitivity lesions mainly contain monocytes and a few T cells.
- Major lymphokines involved in delayed hypersensitivity reaction include monocyte chemotactic factor, interleukin-2,
- interferon, TNF