Type IV Hypersensitivity

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➢ Type IV Hypersensitivity reactions :

• Type lV hypersensitivity, commonly referred to as Delayed Type Hypersensitivity (DTH), is the only hypersensitivity category that is purely cell mediated rather than antibody mediated.

• In 1890, Robert Koch observed that individuals infected with Mycobacterium tuberculosis developed a localized inflammatory response when injected intradermally (in the skin) with a filtrate derived from a mycobacterial culture. He therefore named this localized skin reaction a tuberculin reaction.

• Later, as it became apparent that a variety of other antigens could induce this cellular response (Table 15-6), its name was changed to delayed-type, or type IV, hypersensitivity.

• The hallmarks of a type IV reaction are its initiation by T cells (as distinct from antibodies), the delay required for the reaction to develop, and the recruitment of macrophages (as opposed to neutrophils or eosinophils) as the primary cellular component of the infiltrate that surrounds the site of inflammation.

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

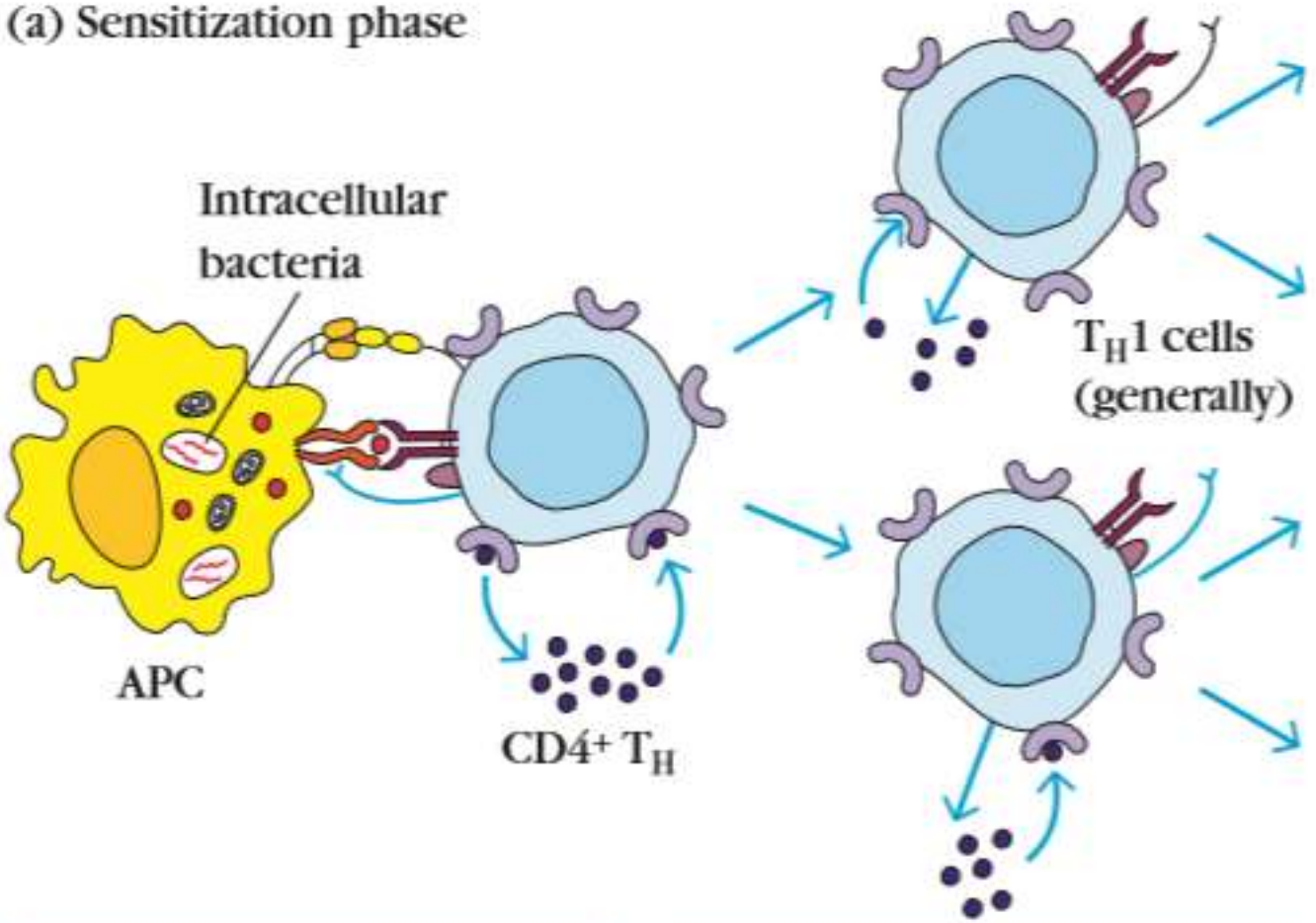
Intracellular bacteria	Intracellular viruses
Mycobacterium tuberculosis	Herpes simplex virus
Mycobacterium leprae	Variola (smallpox)
Brucella abortus	Measles virus
Listeria monocytogenes	
Intracellular fungi	**Contact antigens**
Pneumocystis carinii	Picrylchloride
Candida albicans	Hair dyes
Histoplasma capsulatum	Nickel salts
Cryptococcus neoformans	Poison ivy
	Poison oak
Intracellular parasites	
Leishmania sp.	

• The most common type IV hypersensitivity is the contact dermatitis that occurs after exposure to Toxicodendron species, which include poison ivy, poison oak, and poison sumac.
• This is a significant public health problem. Approximately 50% to 70% of the U.S. adult population is clinically sensitive to exposure to Toxicodendron ; only 10% to 15% of the population is tolerant.
• Some responses can be severe and require hospitalization.

➢ Initiation of DTH response involves sensitization by antigen

• DTH response begins with an initial sensitization by antigen, followed by a period of at least 1 to 2 weeks during which antigen-specific T cells are activated and clonally expanded (Figure 15-14a).

• A variety of antigen- presenting cells (APCs) are involved in the induction of a DTH response, including Langerhans cells (dendritic cells found in the epidermis) and macrophages.



Antigen-presenting cells:
- Macrophages
- Langerhans cells

DTH-mediating cells:
- $CD4^+$ T_H1 generally and T_H17, T_H2, and $CD8^+$ cells occasionally

• These cells pick up antigen that enters through the skin and transport it to regional lymph nodes, where T cells are activated.

• Generally, the T cells activated during the sensitization phase of a traditional DTH response are $CD4^+$, primarily of the T_H1 subtypes.

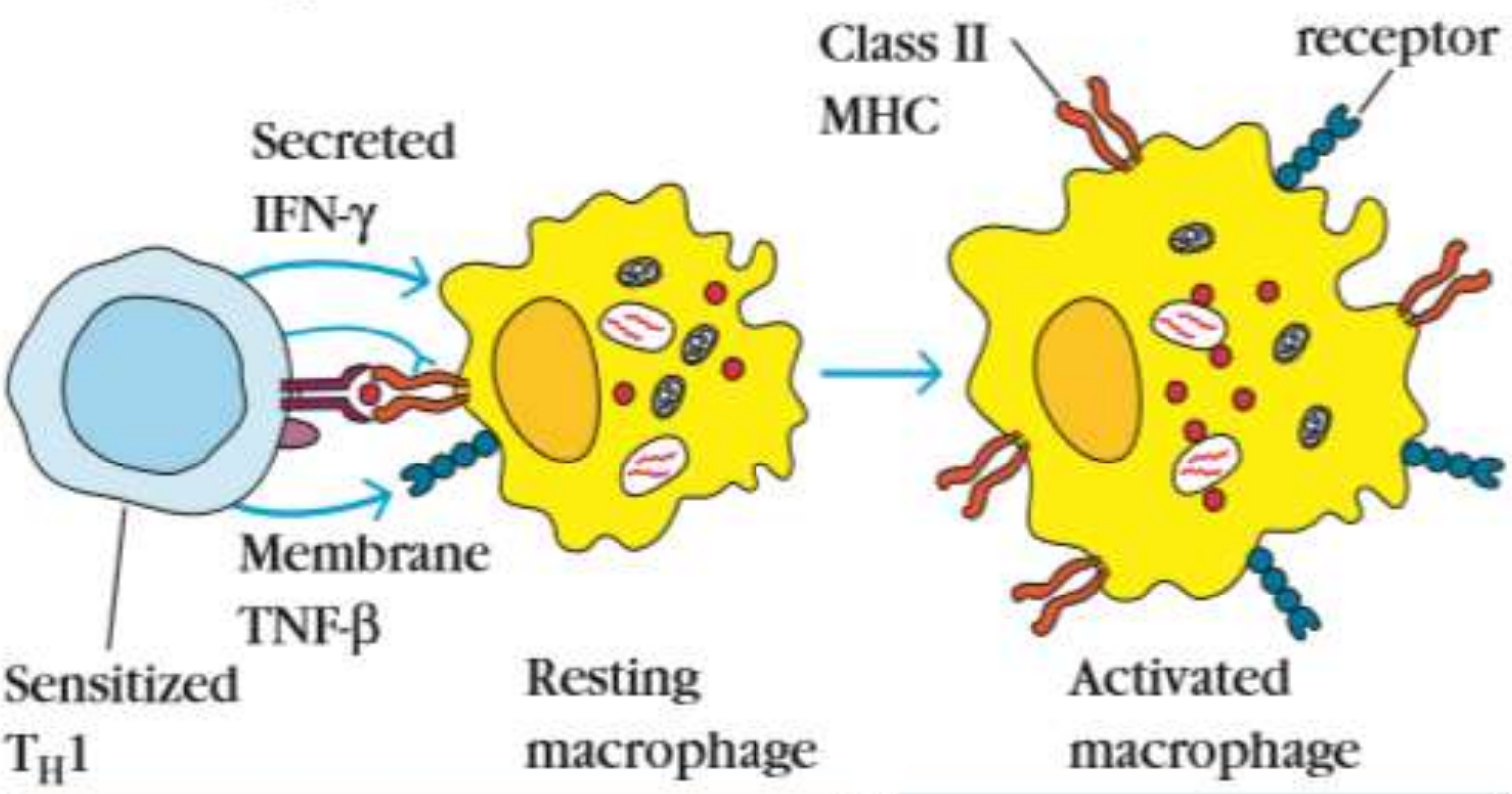
• However, recent studies indicate that T_H17, T_H2, and $CD8^+$ cells can also play a role.

➢ The effector phase of a classical DTH response is induced by second exposure to a sensitizing antigen:

• A second exposure to the sensitizing antigen induces the effector phase of the DTH response (see Figure 15-14b).

• In the effector phase, T cells are stimulated to secrete a variety of cytokines, including interferon- γ (IFN- γ) and Lymphotoxin- α (TNF- β), which recruit and activate macrophages and other inflammatory cells.

(b) Effector phase



T_H1 secretions:

Cytokines: IFN-γ, LT-α (TNF-β), IL-2, IL-3, GM-CSF, MIF

Chemokines: IL-8/CXCL8, MCP-1/CCL2

Effects of macrophage activation:

↑ Class II MHC molecules

↑ TNF receptors

↑ Oxygen radicals

• A DTH response normally does not become apparent until an average of 24 hours after the second contact with the antigen and generally peaks 48 to 72 hours after this stimulus.

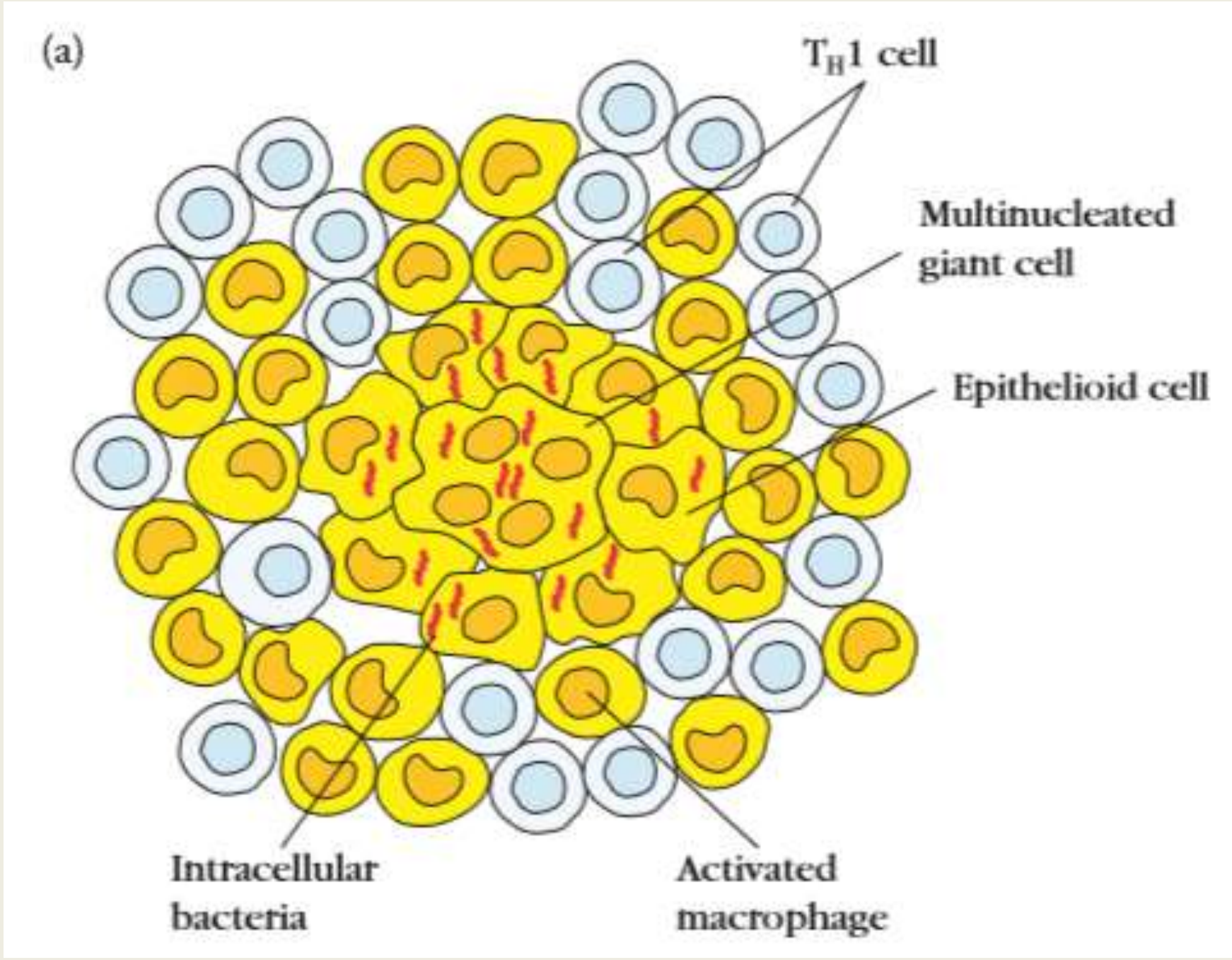
• The delayed onset of this response reflects the time required for the cytokines to induce localized influxes of macrophages and their activation.

• T_H1 cells are important initiators of DTH, but the principal effector cells of the DTH response are activated macrophages.

• Cytokines elaborated by helper T cells, including IFN- γ and Lymphotoxin- α, induce blood monocytes to adhere to vascular endothelial cells, migrate from the blood into the surrounding tissues, and differentiate into activated macrophages.
• Activated macrophages exhibit enhanced phagocytosis and an increased ability to kill microorganisms.
• They produce cytokines, including TNF- α and IL-1β , that recruit more monocytes and neutrophils, and enhance the activity of T_H1 cells, amplifying the response.

• The heightened phagocytic activity and the buildup of lytic enzymes from macrophages in the area of infection lead to nonspecific destruction of cells and thus of any intracellular pathogens, such as Mycobacteria .
• Usually, any presented pathogens are cleared rapidly with little tissue damage.
• However, in some cases, and especially if the antigen is not easily cleared, a prolonged DTH response can develop, which becomes destructive to the host, causing a visible granulomatous reaction.

• Granulomas develop when continuous activation of macrophages induces them to adhere closely to one another.
• Under these conditions, macrophages assume an epithelioid shape and sometimes fuse to form multinucleated giant cells (Figure 15-15a).
• These giant cells displace the normal tissue cells, forming palpable nodules, and releasing high concentrations of lytic enzymes, which destroy surrounding tissue.
• The granulomatous response can damage blood vessels and lead to extensive tissue necrosis.


(a)
T_H1 cell
Multinucleated giant cell
Epithelioid cell
Intracellular bacteria
Activated macrophage

• The response to Mycobacterium tuberculosis illustrates the double-edged nature of the DTH response.
• Immunity to this intracellular bacterium involves a DTH response in which activated macrophages wall off the organism in the lung and contain it within a granuloma-type lesion called a tubercle (see Figure 15-15b).
• Often, however, the release of concentrated lytic enzymes from the activated macrophages within the tubercles damages the very lung tissue that the immune response aims to preserve.

(b)

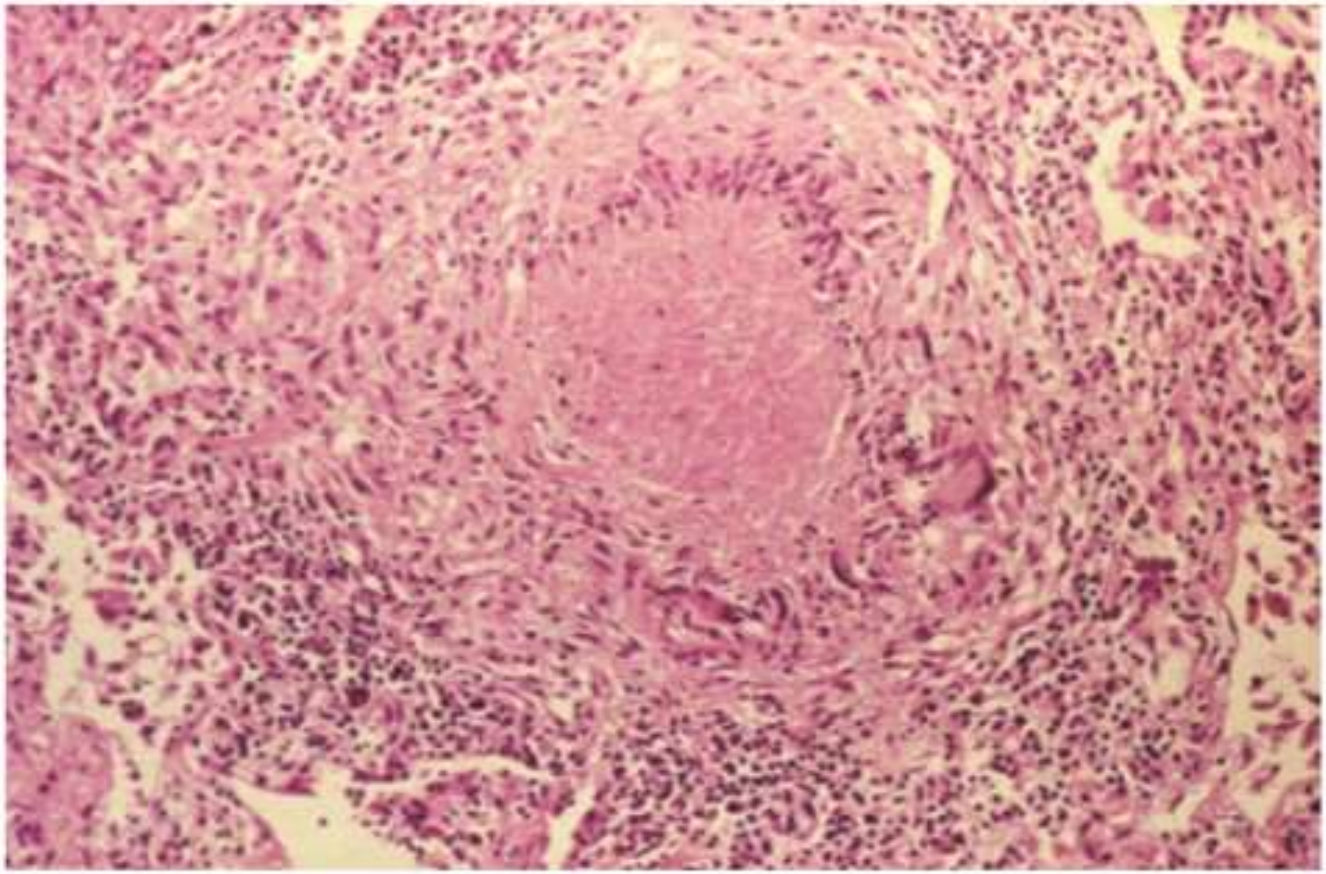


FIGURE 15-15 A prolonged DTH response can lead to formation of a granuloma, a nodule-like mass. (a) Lytic enzymes released from activated macrophages in a granuloma can cause extensive tissue damage. (b) Stained section of a granuloma associated with tuberculosis. *[Biophoto Associates/Getty Images]*

▪ Contact dermatitis: It is one common manifestation of a type IV hypersensitivity.

• The simplest form of contact dermatitis occurs when a reactive chemical compound binds to skin proteins and these modified proteins are presented to T cells in the context of the appropriate MHC antigens.

• The reactive chemical may be a pharmaceutical, a component of a cosmetic or a hair dye, an industrial chemical such as formaldehyde or turpentine, an artificial hapten such as fluoro-dinitrobenzene, a metal ion such as nickel, or the active allergen from poison ivy.

• At present the best way to avoid a DTH response it to avoid the causative antigen.
• Once hypersensitivity has developed, topical or oral corticosteroids can be used to suppress the destructive immune response.