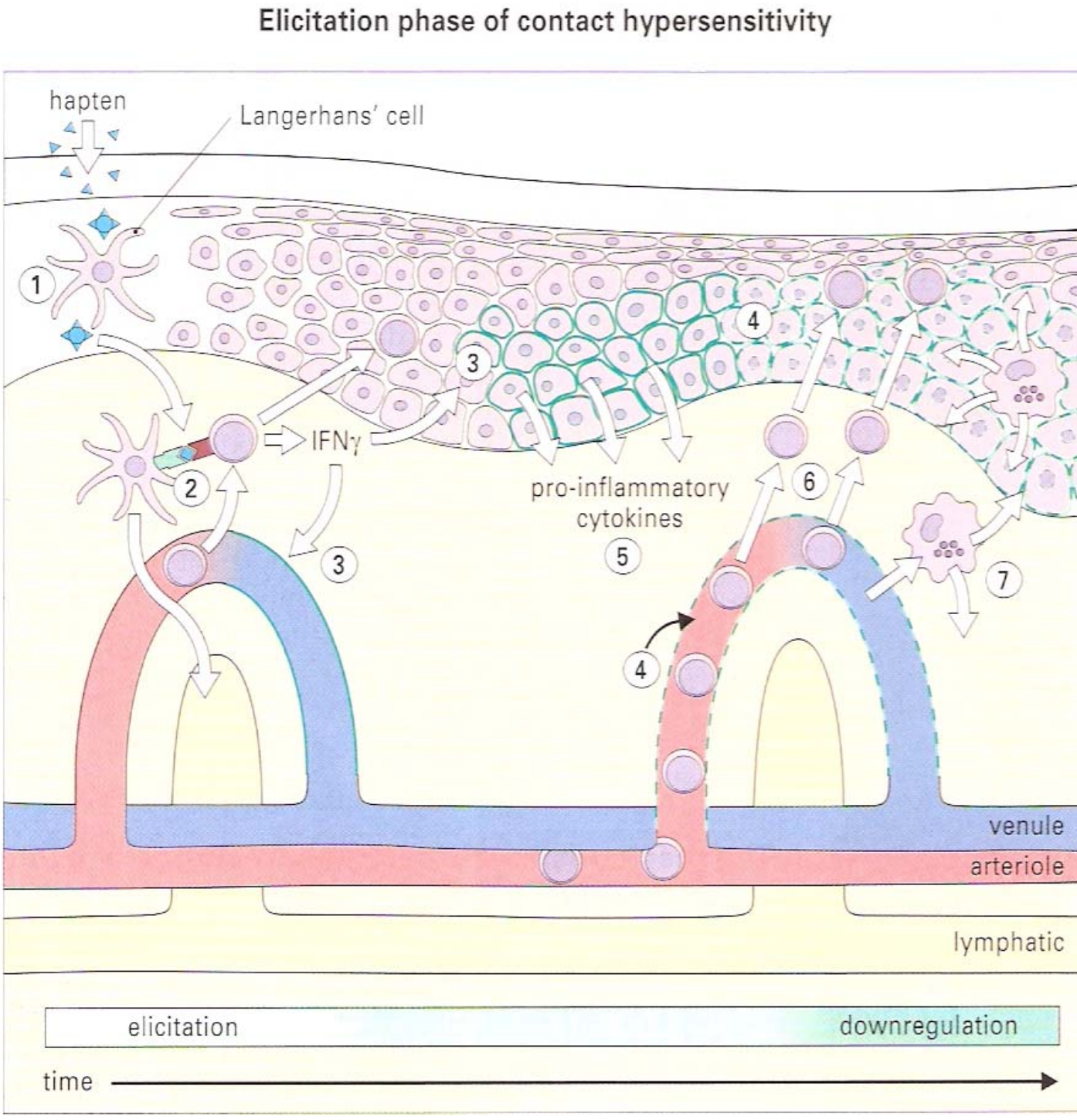


**Figure-5** Langerhans' cells carrying the hapten-carrier complex (1) move from the epidermis to the dermis, where they present the hapten-carrer complex to memory $CD4^+$ T cells (2). Activated $CD4^+$ T cells release IFNγ, which induces expression of ICAM-1 (3) and, later, MHC class II molecules (4) on the surface of keratinocytes and on

endothelial cells of dermal capillaries and activates keratinocytes which release pro-inflammatory cytokines such as IL-1, IL-6 and GM-CSF (5). Non-antigen-specific $CD4^+$ T cells are attracted to the site by cytokines (6) and may bind to keratinocytes via ICAM-1 and class II molecules. Activated macrophages are also attracted to the skin, but this occurs later. Thereafter the reaction starts to down-regulate. This downregulation may be influenced by eicosanoids such as PGE, produced by activated keratinocytes and macrophages (7).

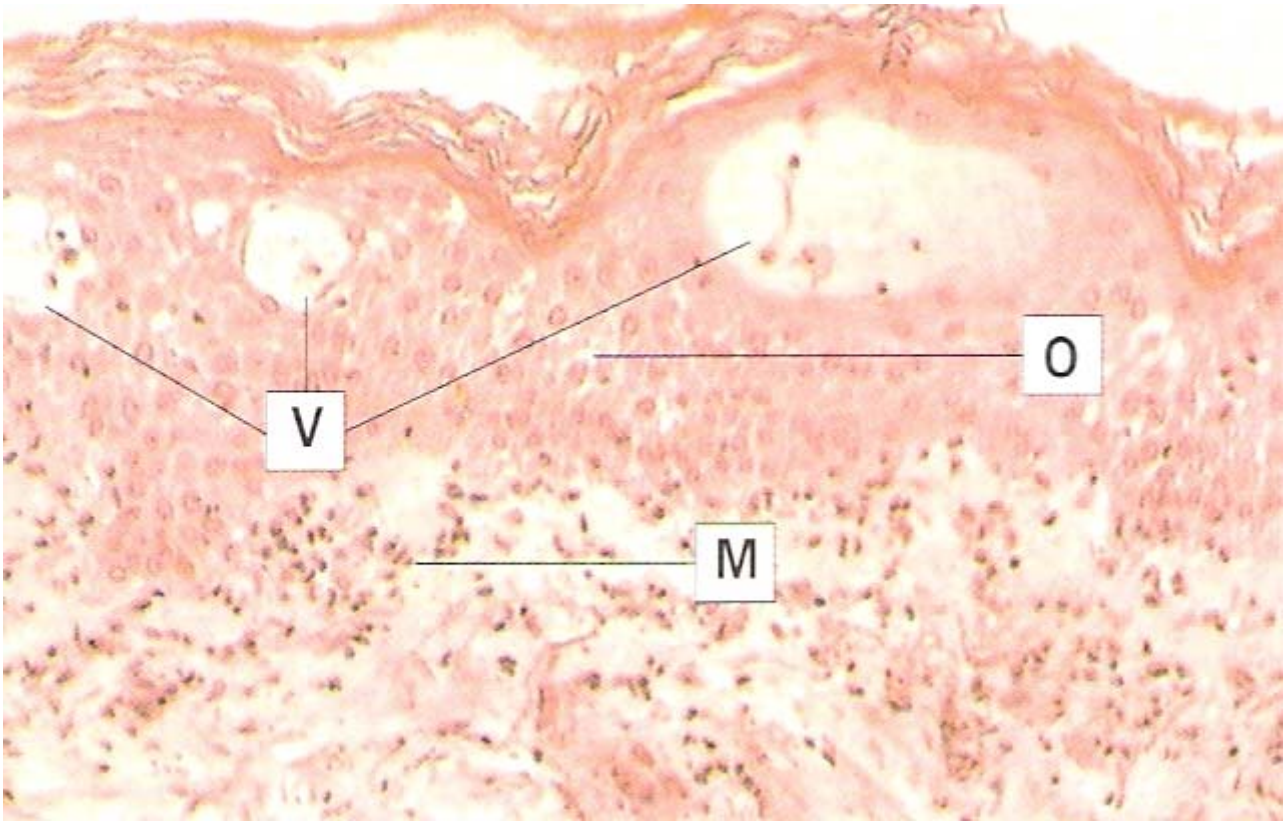


**Figure-6** Histological appearance of the lesion in contact hypersensitivity. Mononuclear cells (M) infiltrate both dermis and epidermis. The epidermis is pushed outwards and microvesicles (V) form within it due to oedema (O). H&E stain, x130.

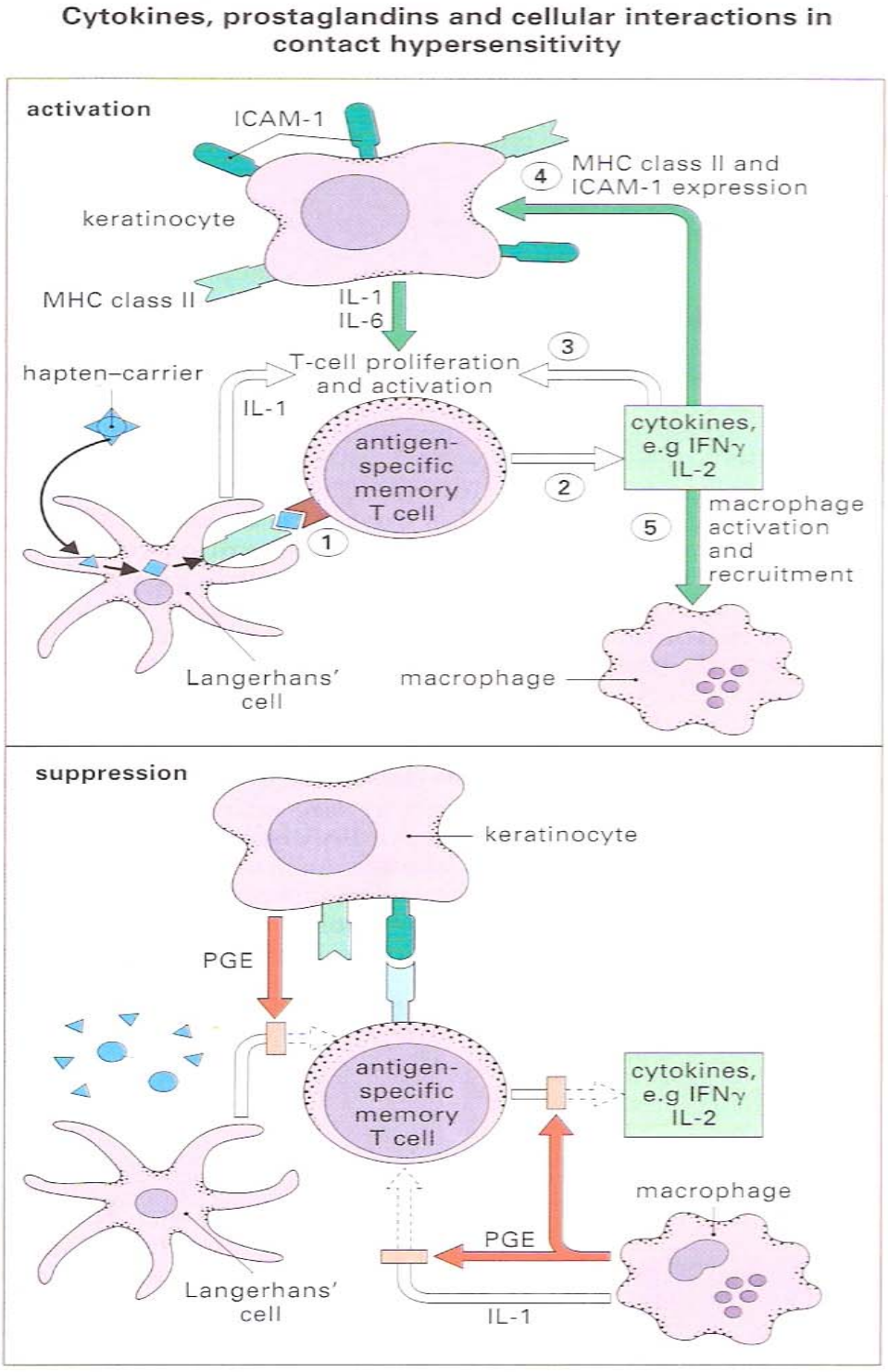


**Figure-7** Cytokines and pro-staglandins are central to the complex interactions between Langerhans' cells, $CD4^{+}$ T cells, keratinocytes, macrophages and endothelial cells in

contact hypersensitivity. The act of antigen presentation (1) causes the release of a cascade of cytokines (2). This cascade initially results in the activation and proliferation of $CD4^+$ T cells (3), the induction of expression of ICAM-1 and MHC class II molecules on keratinocytes and endothelial cells (4), and the attraction of further T cells and macrophages to the skin (3,5). Subsequent PGE production by keratinocytes and macrophages may have an inhibitory effect on IL-1 and IL-2 production. Production of PGE, binding of activated T cells to keratinocytes and enzymatic and cellular degradation of the hapten – carrier complex all contribute to the down-regulation of the reaction.

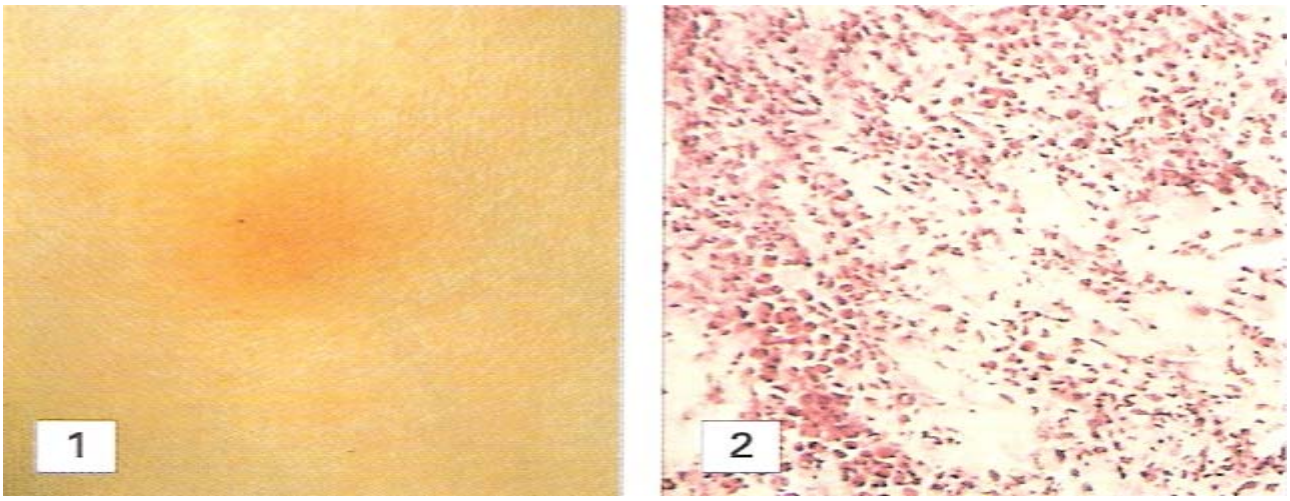


**Figure-8** Clinical and histological appearance of tuberculin-type sensitivity. The response to an injection of leprosy bacillus into a sensitized individual is known as the Fernandez reaction. The reaction is characterized by an area of firm red swelling of the skin and is maximal 48 -72 hours after challenge (1). Histological (2), there is a dense dermal infiltrate of leucocytes H&E stain, x80.

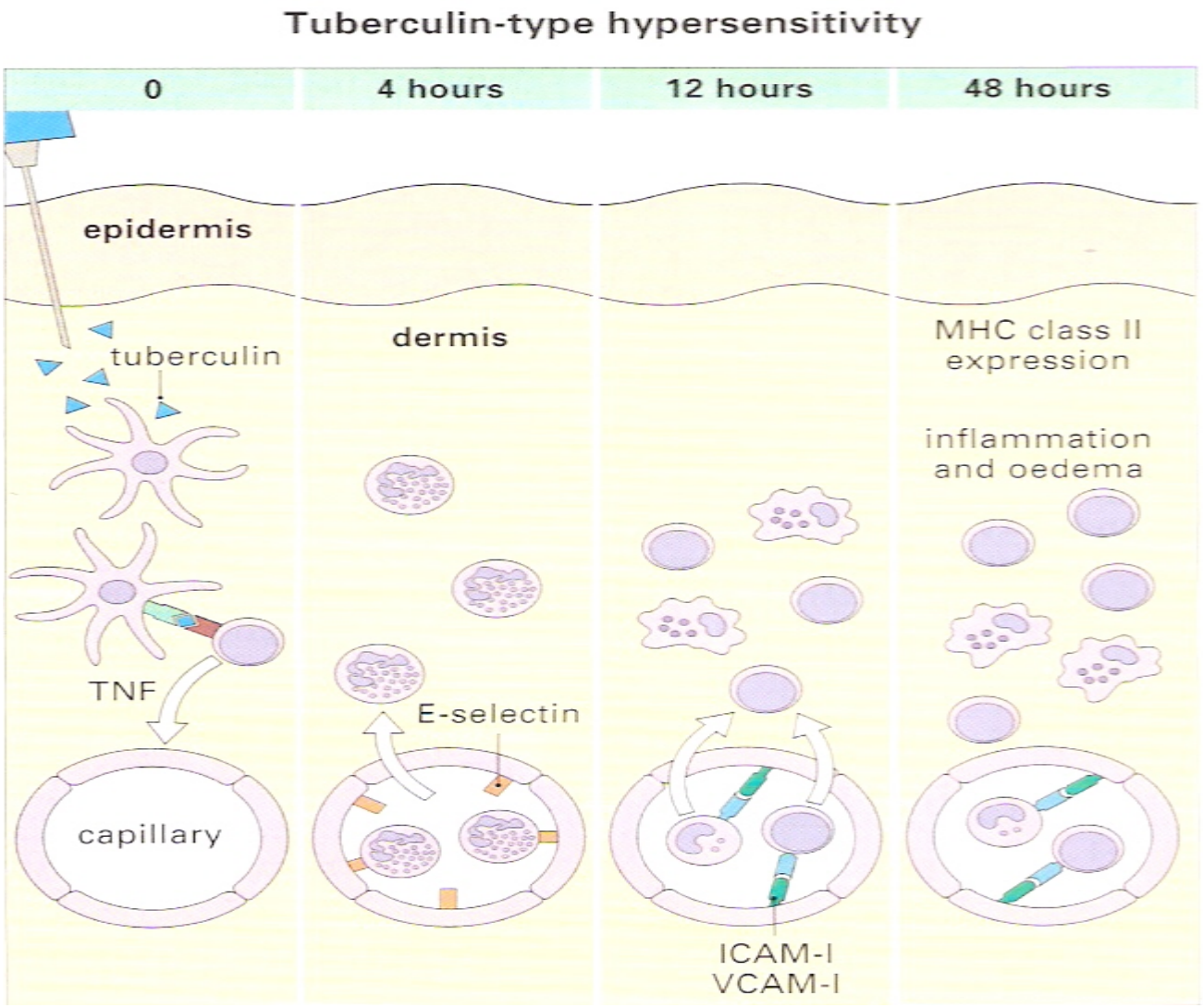


**Figure-9** This diagram illustrates cellular movements following intradermal injection of tuberculin. Within 1-2 hours there is expression of E-selection on capillary endothelium leading to a brief influx of neutrophil leucocytes. By 12 hours ICAM-1 and VCAM-1 on endothelium bind the integrins LFA-1 and VLA-4 on monocytes and lymphocytes, leading to accumulation of both cell types in the dermis. This peaks at 48 hours and is followed by expression of the HLA class II molecules on keratinocytes. There is no oedema of the epidermis.

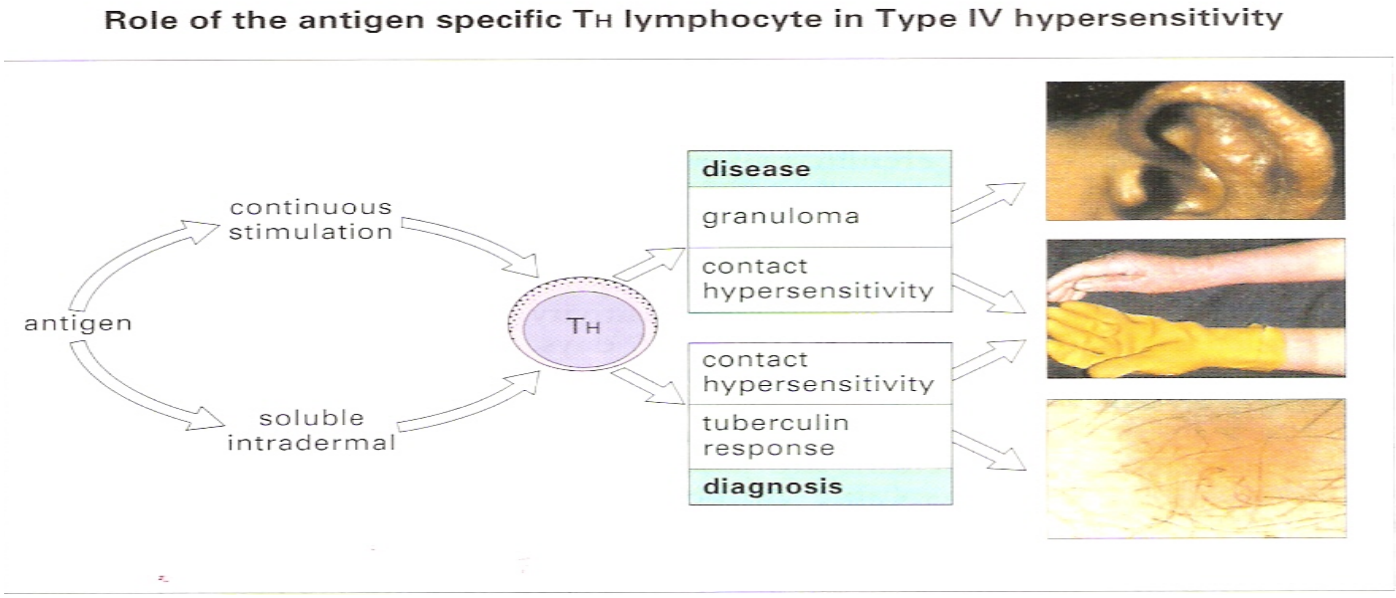


**Figure-10** The tuberculin skin reaction is the classic diagnostic test for cell-mediated immunity in tuberculosis. If there is continuous antigenic stimulation instead of a single injection of soluble antigen, a granulomatous reaction or contact hypersensitivity follows. This granulomatous reaction can also occur if the macrophages cannot destroy the antigen.

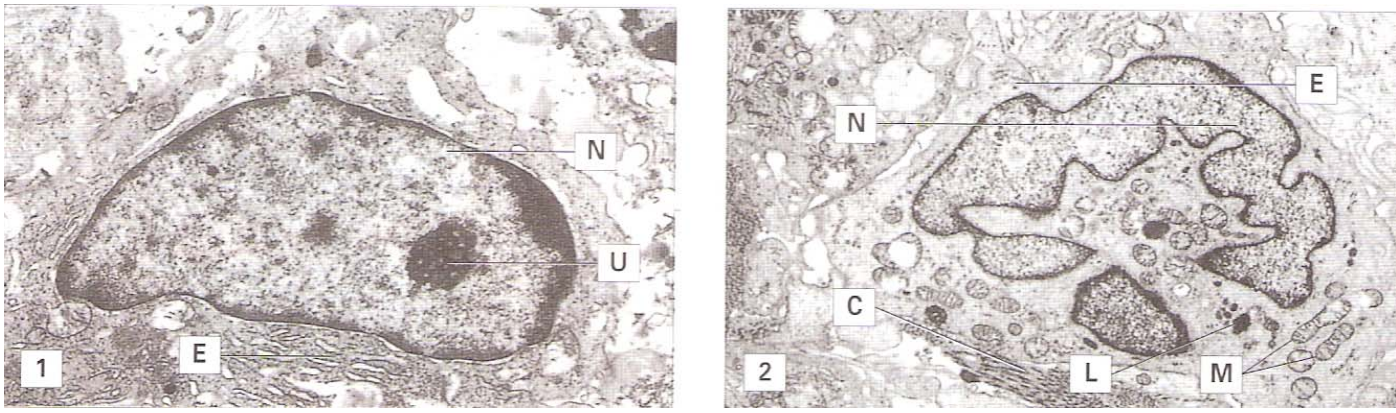


**Figure-11** Electron micrograph of an epithelioid cell shows the characteristic cell of granulomatous hypersensitivity. Compare the extent of the endoplasmic reticulum (E) in the epithelioid cell (1) (x48000) with that of tissue microphones (2) (x48000). U=nucleolus; N=nucleus; C=collagen; L=lysosome; M=mitochondria.

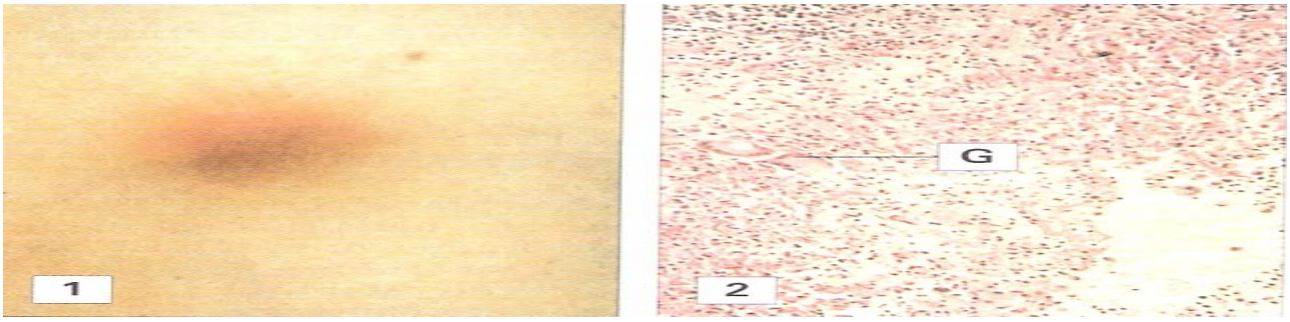


**Figure-12** Clinical and histological appearances of the Mitsuda reaction in leprosy seen at 28 days. (1) The resultant skin swelling (which may be ulcerated) is much harder and better defined than at 48 hours. (2) Histology shows a typical epithelioid-cell granuloma (H&E stain, x60). Giant cells (G) are visible in the centre of the lesion, which is surrounded by a cuff of lymphocytes. This response is more akin to the pathological processes in delayed hypersensitivity diseases than the self-resolving tuberculin-type reaction. The reaction is due to the continued presence of mycobacterial antigen.

**Delayed hypersensitivity reactions**

| type | reaction time | clinical appearance | histology | antigen |
|---|---|---|---|---|
| contact | 48–72 hr | eczema | lymphocytes, later macrophages, oedema of epidermis | epidermal e.g. nickel, rubber, poison ivy |
| tuberculin | 48–72 hr | local induration | lymphocytes, monocytes, macrophages | intradermal e.g. tuberculin |
| granuloma | 21–28 days | hardening e.g. skin or lung | macrophages, epithelioid cells, giant cells, fibrosis | persistent Ag or Ag/Ab complexes or non-immunoglobin stimuli e.g. talc |

**Figure-13** The characteristics of Type IV reactions comparing contact, tuberculin and granulomatous reactions.

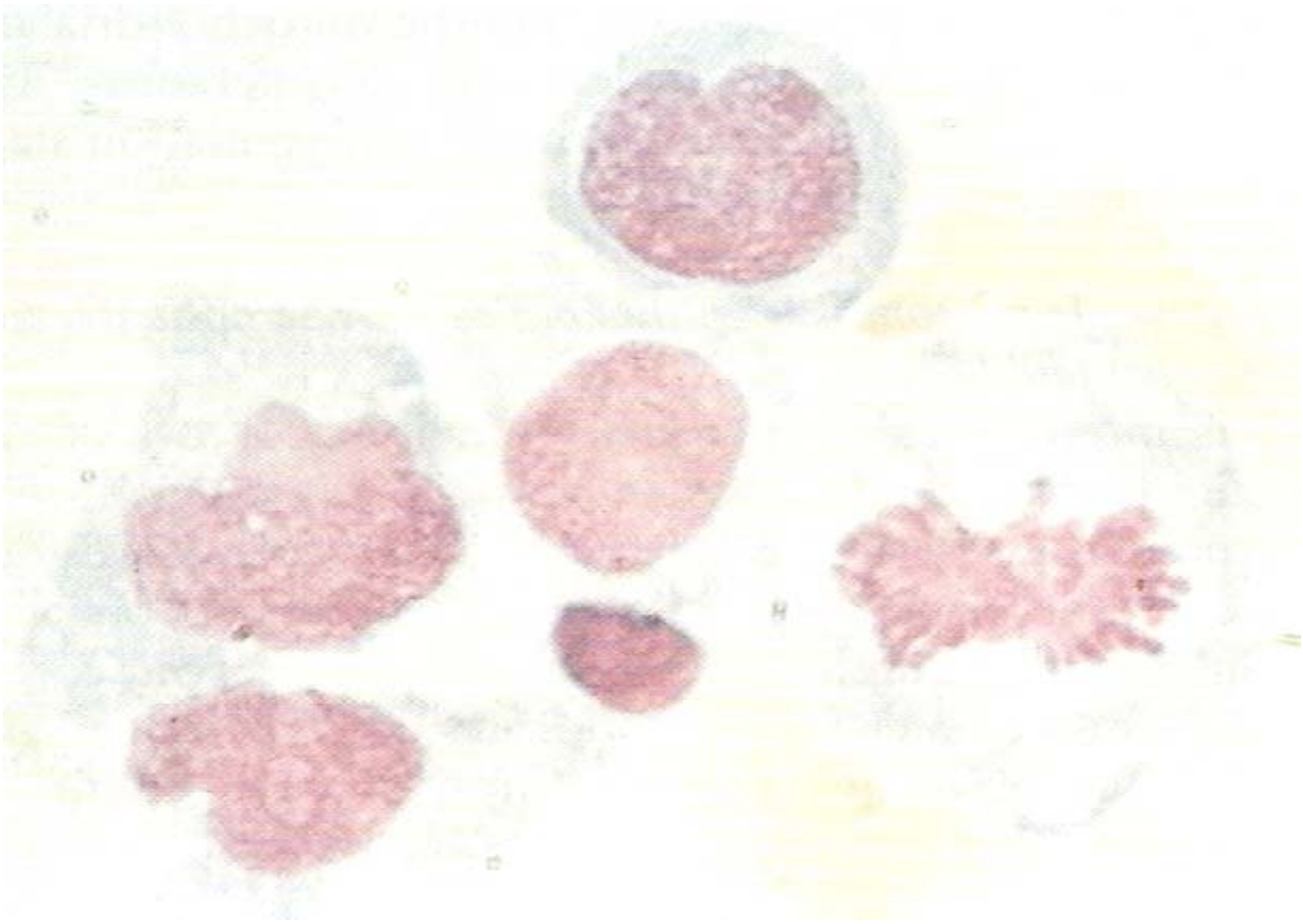

**Figure-14** Transformed lymphocytes. Following stimulation with appropriate antigen, T cells undergo lymphoblastoid transformation prior to cell division. Blast cells with expanded nuclei and cytoplasm (as well as one lymphocyte in the metaphase of cell division) as shown.

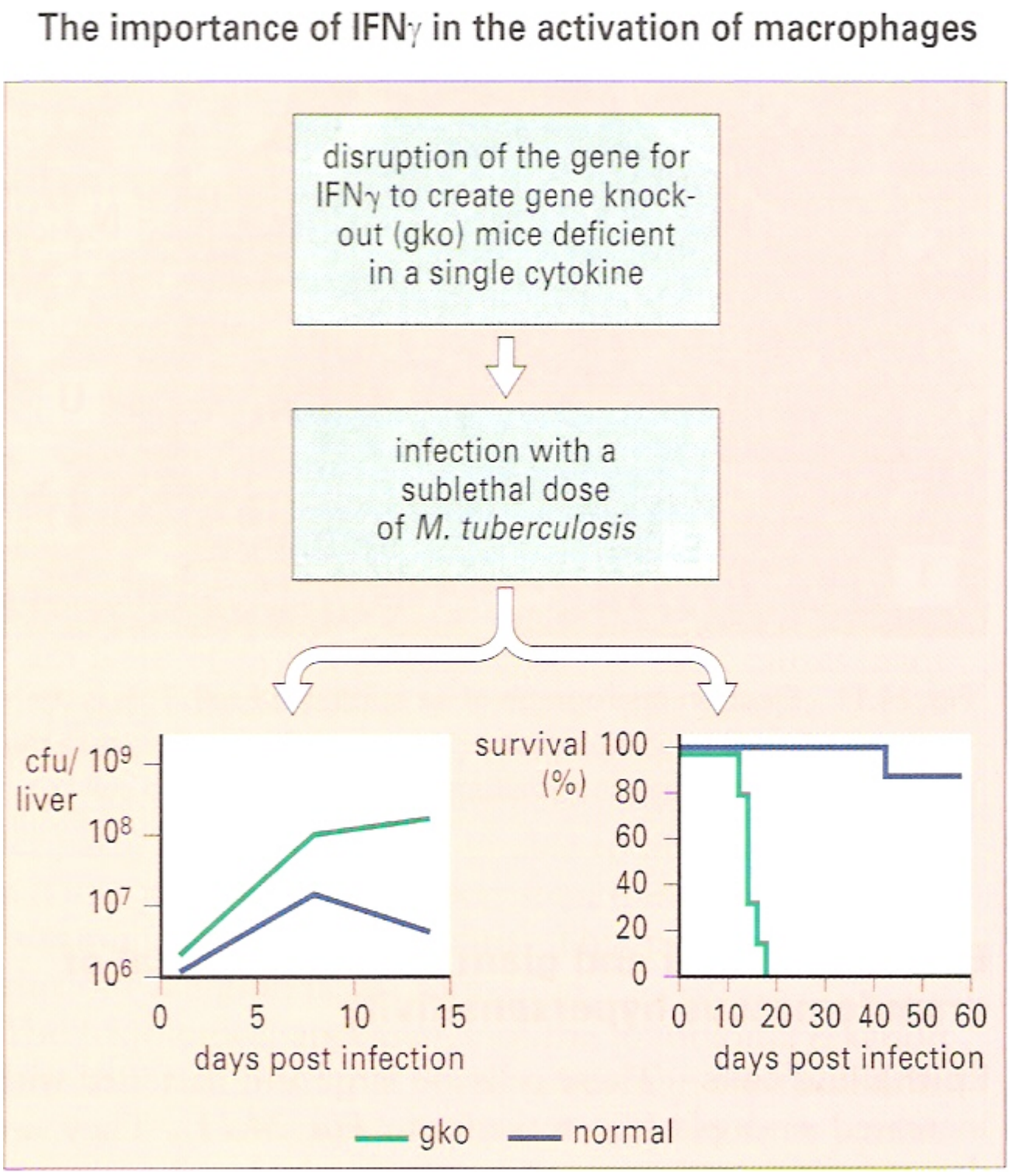


**Figure-15** Mice deficient in IFNγ (gko mice) are unable to activate macrophages in response to infection with an intracellular bacterium. Macrophages initially accumulate at

the site of infection but do not form typical granulomas. Uncontrolled infection (graph, left) causes widespread tissue necrosis and death (graph, right). cfu: colony forming units of infectious agent in the liver.