Chronic Inflammation

Granulomatous Reaction

Tuberculous Granuloma

Other particle induced granulomas

Granulomas of Unknown origin
Chronic Inflammation

Granulomatous Reaction

Tuberculous Granuloma

Other particle induced granulomas

Granulomas of Unknown origin
Chronic inflammation is considered to be inflammation of prolonged duration (weeks or months) in which active inflammation, tissue destruction, and attempts at repair are proceeding simultaneously.
Chronic Inflammation (2)

-it may follow acute inflammation,

-frequently begins insidiously, as a low-grade, smoldering, often asymptomatic response.

-is the cause of tissue damage in some of the most common and disabling human diseases
### Primary Chronic Inflammation

#### Table 10-3. Some examples of primary chronic inflammation

<table>
<thead>
<tr>
<th>Cause of inflammation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance of infective agent to phagocytosis and intracellular killing</td>
<td>Tuberculosis, leprosy, brucellosis, viral infections</td>
</tr>
<tr>
<td>Endogenous materials</td>
<td>Necrotic adipose tissue, bone, uric acid crystals</td>
</tr>
<tr>
<td>Exogenous materials</td>
<td>Silica, asbestos fibres, suture materials, implanted prostheses</td>
</tr>
<tr>
<td>Some autoimmune diseases</td>
<td>Organ-specific disease, e.g. Hashimoto's thyroiditis, chronic gastritis of pernicious anaemia</td>
</tr>
<tr>
<td></td>
<td>Non-organ-specific autoimmune disease, e.g. rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>Contact hypersensitivity reactions, e.g. self-antigens altered by nickel</td>
</tr>
<tr>
<td>Specific diseases of unknown aetiology</td>
<td>Chronic inflammatory bowel disease, e.g. ulcerative colitis</td>
</tr>
<tr>
<td>Primary granulomatous diseases</td>
<td>Crohn's disease, sarcoidosis, reactions to beryllium</td>
</tr>
</tbody>
</table>
## Chronic Inflammation (4)

### MORPHOLOGIC FEATURES

<table>
<thead>
<tr>
<th>ACUTE INFLAMMATION</th>
<th>CHRONIC INFLAMMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>is manifested by <em>vascular changes, edema, and predominantly neutrophilic infiltration</em></td>
<td>is characterized by:</td>
</tr>
<tr>
<td></td>
<td>- Infiltration with <em>mononuclear cells</em>, which include macrophages, lymphocytes, and plasma cells.</td>
</tr>
<tr>
<td></td>
<td>- <em>Tissue destruction</em>, induced by the persistent offending agent or by the inflammatory cells.</td>
</tr>
<tr>
<td></td>
<td>- Attempts at <em>healing by connective tissue replacement of damaged tissue</em>, accomplished by proliferation of small blood vessels (<em>angiogenesis</em>) and, in particular, <em>fibrosis</em>.</td>
</tr>
</tbody>
</table>
Chronic inflammation in the lung, showing all three characteristic histologic features: (1) collection of chronic inflammatory cells, (2) destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium, arrowheads), and (3) replacement by connective tissue (fibrosis, arrows).

Acute inflammation of the lung (acute bronchopneumonia), neutrophils fill the alveolar spaces and blood vessels are congested.
Chronic Inflammation

Granulomatous Reaction and Formation

Tuberculous Granuloma

Other particle induced granulomas

Granulomas of Unknown origin
Chronic Inflammation (6)

- *Infiltration with mononuclear cells*  
  (macrophages, lymphocytes, and plasma cells)

- *Tissue destruction*  
  (induced by the persistent offending agent or by the inflammatory cells)

- *Attempts at healing by connective tissue replacement of damaged tissue,*  
  proliferation of small blood vessels, i.e. angiogenesis and, fibrosis)
Infiltration of mononuclear cells in Chronic Inflammation
**Monocytes - Macrophages**

- **Bone marrow**: Stem cell → Monoblast → Monocyte
- **Blood**: Monocyte → Macrophage
- **Tissues**: Microglia (CNS), Kupffer cells (liver), Alveolar macrophages (lung), Osteoclasts (bone)

Activated macrophage

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Mononuclear Cells Migration
In short-lived inflammation, if the irritant is eliminated, macrophages eventually disappear (either dying off or making their way into the lymphatics and lymph nodes).
In chronic inflammation, macrophage accumulation persists.

**Recruitment of monocytes from the circulation**, (chemotactic factors produced by activated macrophages, lymphocytes, and other cell types (e.g., MCP-1); C5a; growth factors such as platelet-derived growth factor and transforming growth factor-α (TGF-α); fragments from the breakdown of collagen and fibronectin; and fibrinopeptides).

**Local proliferation of macrophages**
Once thought to be an unusual event, macrophage proliferation is now known to occur prominently in some chronic inflammatory lesions, such as atheromatous plaques.

**Immobilization of macrophages within the site of inflammation.**
Certain cytokines and oxidized lipids can cause such immobilization.
Macrophage accumulation

Chemotactic mediators (cytokines, others)

Recruitment → Division → Immobilization

Cytokines

Collection of macrophages
Chronic Inflammation
Immunoreaction – Tissue Damage
Granuloma Formation

The products of activated macrophages serve to eliminate injurious agents such as microbes and to initiate the process of repair, and are responsible for much of the tissue injury in chronic inflammation.

- Some of these products are toxic to microbes and host cells (e.g., reactive oxygen and nitrogen intermediates) or extracellular matrix (proteases);
- Some cause influx of other cell types (e.g., cytokines, chemotactic factors);
- Others cause fibroblast proliferation, collagen deposition, and angiogenesis.

This impressive arsenal of mediators makes macrophages powerful allies in the body's defense against unwanted invaders, but the same weaponry can also induce considerable tissue destruction when macrophages are inappropriately activated.
Chronic Inflammation

Immunoreaction – Tissue Damage

Granuloma Formation

**Tissue Injury**
- Toxic oxygen metabolites
- Proteases
- Neutrophil chemotactic factors
- Coagulation factors
- AA metabolites
- Nitric oxide

**Fibrosis**
- Growth factors (PDGF, FGF, TGFβ)
- Fibrogenic cytokines
- Angiogenesis factors (FGF)
- "Remodeling" collagenesis
Chronic Inflammation
Immunoreaction – Tissue Damage
Granuloma Formation

Table 10-4. Growth factors involved in healing and repair associated with inflammation

<table>
<thead>
<tr>
<th>Growth factor</th>
<th>Abbreviation</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal growth factor</td>
<td>EGF</td>
<td>Regeneration of epithelial cells</td>
</tr>
<tr>
<td>Transforming growth factor α</td>
<td>TGFα</td>
<td>Regeneration of epithelial cells</td>
</tr>
<tr>
<td>Transforming growth factor β</td>
<td>TGFβ</td>
<td>Stimulates fibroblast proliferation and collagen synthesis Controls epithelial regeneration</td>
</tr>
<tr>
<td>Platelet-derived growth factor</td>
<td>PDGF</td>
<td>Mitogenic and chemotactic for fibroblasts and smooth muscle cells</td>
</tr>
<tr>
<td>Fibroblast growth factor</td>
<td>FGF</td>
<td>Stimulates fibroblast proliferation, angiogenesis and epithelial cell regeneration</td>
</tr>
<tr>
<td>Insulin-like growth factor-1</td>
<td>IGF-1</td>
<td>Synergistic effect with other growth factors</td>
</tr>
<tr>
<td>Tumour necrosis factor</td>
<td>TNF</td>
<td>Stimulates angiogenesis</td>
</tr>
</tbody>
</table>
Chronic Inflammation  
Immunoreaction – Tissue Damage  
Granuloma Formation  

Tissue destruction  
is one of the hallmarks  
of chronic inflammation
Granulomatous Reaction and Formation

Granulomatous inflammation is a distinctive pattern of chronic inflammatory reaction characterized by focal accumulations of activated macrophages, which often develop an epithelial-like (epithelioid) appearance.

- It is encountered in a limited number of immunologically mediated, infectious and some noninfectious conditions.

- Its genesis is firmly linked to immune reactions

- Tuberculosis is the prototype of the granulomatous diseases, but sarcoidosis, cat-scratch disease, lymphogranuloma inguinale, leprosy, brucellosis, syphilis, some mycotic infections, berylliosis, and reactions of irritant lipids are also included
Granulomatous Reaction and Formation

Table 10-5. Causes of granulomatous disease

<table>
<thead>
<tr>
<th>Cause</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific infections</td>
<td>Mycobacteria, e.g. tuberculosis, leprosy, atypical mycobacteria</td>
</tr>
<tr>
<td></td>
<td>Many types of fungi</td>
</tr>
<tr>
<td></td>
<td>Parasites, larvae, eggs and worms</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td>Foreign bodies</td>
<td>Endogenous, e.g. keratin, necrotic bone, cholesterol crystals, sodium urate</td>
</tr>
<tr>
<td></td>
<td>Exogenous, e.g. talc, silica, suture materials, oils, silicone</td>
</tr>
<tr>
<td>Specific chemicals</td>
<td>Beryllium</td>
</tr>
<tr>
<td>Drugs</td>
<td>Hepatic granulomas due to allopurinol, phenylbutazone, sulphonamides</td>
</tr>
<tr>
<td>Unknown</td>
<td>Crohn's disease</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Wegener's granulomatosis</td>
</tr>
</tbody>
</table>
**Granulomatous Reaction and Formation**

**Table 2-7. Examples of Diseases with Granulomatous Inflammations**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cause</th>
<th>Tissue Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Noncaseating tubercle (granuloma prototype): a focus of epithelioid cells, rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cell; caseating tubercle: central amorphous granular debris, loss of all cellular detail; acid-fast bacilli</td>
</tr>
<tr>
<td>Leprosy</td>
<td><em>Mycobacterium leprae</em></td>
<td>Acid-fast bacilli in macrophages; non-caseating granulomas</td>
</tr>
<tr>
<td>Syphilis</td>
<td><em>Treponema pallidum</em></td>
<td>Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells are necrotic without loss of cellular outline</td>
</tr>
<tr>
<td>Cat-scratch disease</td>
<td>Gram-negative bacillus</td>
<td>Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon</td>
</tr>
</tbody>
</table>
Granulomatous Reaction and Formation
Granulomatous Reaction and Formation
Granulomatous Reaction

• Granuloma formation
  – complex and dynamic process
  – diverse cell types

• Four phases of granuloma formation
  – Initiation phase - macrophages attracted to persistent inflammatory stimulus, nucleate granulomatous lesion.
  – Accumulation phase - CD4+ T cells accumulate at the site and recruit other effector cells (T cells, macrophages, eosinophils).
  – Effector phase - During the effector phase, various effector cells attempt to reduce the pathogen load through diverse mechanisms.
  – Resolution Phase - once threat from pathogen is eliminated infiltrating cell population is reduced and the formation of scar tissue occurs.
Granulomatous Reaction

• Delayed type hypersensitivity
  – Primarily response to chronic infections with persistent pathogens
  – Acute infections (*Salmonella, Listeria*)
• Contains pathogen
• Chronic granulomatous inflammation → damage and fibrosis
• Without inciting stimulus or clear benefit to the host (*Sarcoid, Crohn’s, Wegeners, Rheumatoid arthritis*)
• Foreign body reaction e.g. suture
Granulomatous Reaction and Formation

Granuloma with epitheliod and lymphocyte reaction

Granuloma with Caseous Necrosis
### Confusing Terms in Inflammations

<table>
<thead>
<tr>
<th>Commonly confused</th>
<th>Distinction and explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute and chronic</td>
<td>In inflammation, acute and chronic denote both the dynamics and character of the process. Acute inflammation has a relatively rapid onset and, usually, resolution, and neutrophil polymorphs are the most abundant cells. Chronic inflammation has a relatively insidious onset, prolonged course and slow resolution, and lymphocytes, plasma cells and macrophages (sometimes with granuloma formation) are the most abundant cells.</td>
</tr>
<tr>
<td>Exudate and transudate</td>
<td>Exudates have a high protein content because they result from increased vascular permeability. Transudates have a low protein content because the vessels have normal permeability characteristics.</td>
</tr>
<tr>
<td>Granuloma and granulation tissue</td>
<td>A granuloma is an aggregate of epithelioid histiocytes and a feature of some specific chronic inflammatory disorders. Granulation tissue is an important component of healing and comprises small blood vessels in a connective tissue matrix with myofibroblasts.</td>
</tr>
<tr>
<td>Monocytes, macrophages and histiocytes</td>
<td>Monocytes are the newly-formed cells of the mononuclear phagocyte system. After a few hours in the blood, they enter tissues and undergo further differentiation into macrophages. Some macrophages in tissues have specific features and names (e.g. Kupffer cells); others are referred to as histiocytes.</td>
</tr>
<tr>
<td>Fibrin and fibrous</td>
<td>Fibrin is deposited in blood vessels and tissues or on surfaces (e.g. in acute inflammation) as a result of the action of thrombin on fibrinogen. Fibrous describes the texture of a non-mineralised tissue of which the principal component is collagen (e.g. scar tissue).</td>
</tr>
</tbody>
</table>
Cell-Mediated (Type IV) Hypersensitivity

and

Delayed Type Hypersensitivity (DTH)
Cell-Mediated (Type IV) Hypersensitivity

The cell-mediated type of hypersensitivity is initiated by antigen-activated (sensitized) T lymphocytes.

It is the principal pattern of immunologic response not only to a variety of intracellular microbiologic agents, such as *Mycobacterium tuberculosis*, but also to many viruses, fungi, protozoa, and parasites. So-called contact skin sensitivity to chemical agents and graft rejection are other instances of cell-mediated reactions. In addition, many autoimmune diseases are now known to be caused by T cell-mediated reactions.

It includes the *delayed type hypersensitivity reactions* mediated by CD4+ T cells, and *direct cell cytotoxicity* mediated by CD8+ T cells.
The classic example of delayed hypersensitivity is the **tuberculin reaction**, which is produced by the intracutaneous injection of tuberculin, a protein-lipopolysaccharide component of the tubercle bacillus. *In a previously sensitized individual, reddening and induration of the site appear in 8 to 12 hours, reach a peak in 24 to 72 hours, and thereafter slowly subside.*

-Morphologically, delayed type hypersensitivity is characterized by the accumulation of mononuclear cells around small veins and venules, producing a perivascular "cuffing".
-There is an associated increased microvascular permeability caused by mechanisms similar to those in other forms of inflammation. Not unexpectedly, plasma proteins escape, giving rise to dermal edema and deposition of fibrin in the interstitium.
-The latter appears to be the main cause of induration, which is characteristic of delayed hypersensitivity skin lesions.
-Immunoperoxidase staining of the lesions reveals a preponderance of CD4+ (helper) T lymphocytes.
Delayed Type Hypersensitivity
Perivascular infiltration by T cells and mononuclear phagocytes.

Immunoperoxidase staining reveals a predominantly perivascular cellular infiltrate that marks positively with anti-CD4 antibodies.
Delayed Type Hypersensitivity
With certain persistent or nondegradable antigens, such as tubercle bacilli colonizing the lungs or other tissues, the initial perivascular lymphocytic infiltrate is replaced by macrophages over a period of 2 or 3 weeks. The accumulated macrophages often undergo a morphologic transformation into epithelium-like cells and are then referred to as *epithelioid cells*. A microscopic aggregation of epithelioid cells, usually surrounded by a collar of lymphocytes, is referred to as a *granuloma*. This pattern of inflammation that is sometimes seen in type IV hypersensitivity is called *granulomatous inflammation*. 

### Delayed Type Hypersensitivity and Granuloma
Chronic Inflammation

Granulomatous Reaction and Formation

Tuberculous Granuloma

Other particle induced granulomas

Granulomas of Unknown origin
TB - introduction

- Infects one third of world population..
- About 3 million deaths due to TB every year
- Under privileged population
- Crowding, Poverty, malnutrition,
- Since 1985 incidence is increasing in west
- AIDS, Diabetes, Immunosuppressed patients, Diabetes
- Drug resistance.
Microbiology of TB

- Mycobacteria – ‘fungus like..
- Bacilli, Aerobic, non motile, no toxins, no spore.
- Mycolic acid wax in cell wall
- Carbol dye - Acid & alcohol fast (AFB)
AFB - Ziehl-Nielsen stain
Innate Immunity

Expression of IL-1, IL-6, TNF-α and NO

Delayed Type Hypersensitivity

Mycobacterium tuberculosis
Antigenic expression (virulence and transcriptional factors, metabolic adaptation to the host etc.)

Specific T-cell response
Expression of IL-2, IFN-γ and TNF-α

x% resolve infection

5% can develop disease within the first 2 years

5% can develop disease long-life
Intracellular lifestyle of MTB

Kaufmann SHE, Nat. Rev. Immunol 2001
Antigenic processing/presentation pathways and activation of different T-cell subsets during MTB infection

Kaufmann SHE, Nat. Rev. Immunol 2001
Different T-cell subsets are involved in the control of MTB infection
Type-1 cytokines produced by different T-cell subsets contribute to activate alveolar macrophages to kill MTB and control infection.
Pathogenesis of TB

• Type IV hypersensitivity – T cells – Macrophages $\rightarrow$ Granuloma
• Activated macrophages – *epithelioid cells*
• Remain viable inside macrophages (Mycolic acid wax coat)
• Cord Factor - surface glycolipid Antigenic.
TB Pathogenesis

- Bacterial entry
- T Lymphocytes.
- Macrophages.
- Epitheloid cells.
- Proliferation.
- Central Necrosis.
- Giant cell formation.
- Fibrosis.
Pathogenesis of TB:

Infection - Immunity
Morphology of Granuloma

1. Rounded tight collection of chronic inflammatory cells.
2. Central Caseous necrosis.
3. Active macrophages - epithelioid cells.
4. Outer layer of lymphocytes, plasma cells & fibroblasts.
5. Langhans giant cells – joined epithelioid cells.
Tuberculous Granuloma
Epitheloid cells in Granuloma
Primary tuberculosis

• In a non immunized individual – children* adult*
• Lesion in subpleural zone of lung – can be at other sites*
• Brief acute inflammation – neutrophils.
• 5-6 days invoke granuloma formation.
• 2 to 8 weeks – healing – Ghon focus (+ lymph node → Ghon complex)
• Develop immunity – Mantoux positive
Primary or Ghon’s Complex

• Primary tuberculosis is the pattern seen with initial infection with tuberculosis in children.
• Reactivation, or secondary tuberculosis, is more typically seen in adults.
Ghon Complex
Primary Tuberculosis

In Non Immunized individuals (Children)

• **Primary Tuberculosis:**
  – Self Limited disease
  – Ghons focus, complex or Primary complex.

• **Primary Progressive TB**
  – Miliary TB and TB Meningitis.
  – Common in malnourished children
  – 10% of adults, Immuno-suppressed individuals
Miliary TB Lung
Secondary Tuberculosis:

- Post Primary in immunized individuals.
- Cavitary Granulomatous response.
- Reactivation or Reinfection
- Apical lobes or upper part of lower lobes – $O_2$
- Caseation, cavity - soft granuloma
- Pulmonary or extra-pulmonary
- Local or systemic spread / Miliary
  - Vein – via left ventricle to whole body
  - Artery – miliary spread within the lung
Secondary Tuberculosis:

- Reactivation occurs in 10-15% of patients.
- Most commonly males 30-50 y
- Slowly Progressive (several months)
- Cough, sputum, Low grade fever, night sweats, fatigue and weight loss.
- Hemoptysis or pleuritic pain = severe disease
Typical cavitating granuloma
Cavitary Tuberculosis

- When necrotic tissue is coughed up → cavity.
- Cavitation is typical for large granulomas.
- Cavitation is more common in the secondary reactivation tuberculosis - upper lobes.
Lung TB - Cavitation
Tuberculosis transmission and progression to active disease from latent infection

### Tuberculin skin test

<table>
<thead>
<tr>
<th>Positive TST</th>
<th>Active TB disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latent TB infection</td>
</tr>
<tr>
<td></td>
<td>Recent exposure to <em>M. tuberculosis</em></td>
</tr>
<tr>
<td></td>
<td>Exposure to environmental mycobacteria</td>
</tr>
<tr>
<td></td>
<td>BCG-vaccination</td>
</tr>
</tbody>
</table>

**TST does not distinguish among all these different clinical situations**
TST reaction is maintained by MTB-specific Th1 lymphocytes secreting IFN-γ
IFN-γ produced after M. tuberculosis antigens stimulation can be used as marker equivalent to skin test
M. tuberculosis H37Rv
4,411,529 bp

Mycobacterial antigens

M. tuberculosis
M. bovis BCG vaccine strain
ESAT-6 and CFP10
Environmental mycobacteria

Whole blood (diluted or undiluted)/peripheral blood mononuclear cells
Incubation (overnight or 5-6 days)
Sensitised T cells release IFNγ
IFNγ production measured using
ELISA (e.g., QuantiFERON-TB)
Results expressed as IFNγ (e.g., pg/mL or IU/mL)
ELISPOT (e.g., T SPOT-TB)
Results expressed as number of IFNγ secreting T cells (spot-forming cells)

Mycobacteria tuberculosis antigens (e.g., FPD, ESAT6, CFP10, MPT64)
# Species specificity of ESAT-6 and CFP-10

<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>Antigens</th>
<th>Environmental strains</th>
<th>Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESAT</td>
<td>CFP</td>
<td>ESAT</td>
</tr>
<tr>
<td>M tuberculosis</td>
<td>+</td>
<td>+</td>
<td>M abcessus</td>
</tr>
<tr>
<td>M africanum</td>
<td>+</td>
<td>+</td>
<td>M avium</td>
</tr>
<tr>
<td>M bovis</td>
<td>+</td>
<td>+</td>
<td>M branderi</td>
</tr>
<tr>
<td>BCG substrain</td>
<td></td>
<td></td>
<td>M celatum</td>
</tr>
<tr>
<td>gothenburg</td>
<td>-</td>
<td>-</td>
<td>M cheloneae</td>
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<tr>
<td>moreau</td>
<td>-</td>
<td>-</td>
<td>M fortuitum</td>
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<tr>
<td>tice</td>
<td>-</td>
<td>-</td>
<td>M gordonii</td>
</tr>
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<td>tokyo</td>
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<td>-</td>
<td>M intracellulare</td>
</tr>
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<td>-</td>
<td>M kansasii</td>
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<tr>
<td>glaxo</td>
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<td>M malmoense</td>
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<td>montreal</td>
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<td>-</td>
<td>M marinum</td>
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<td>pasteur</td>
<td>-</td>
<td>-</td>
<td>M oenavense</td>
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<td></td>
<td></td>
<td>M scrofulaceum</td>
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<td>M smegmatis</td>
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<td></td>
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<td></td>
<td>M szulgai</td>
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<td></td>
<td></td>
<td></td>
<td>M terrae</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M vaccae</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M xenopi</td>
</tr>
</tbody>
</table>
Effect of antigens on sensitivity and specificity of IFN-γ assays

PPD

ESAT-6 or CFP-10

ESAT-6 plus CFP-10

Chronic Inflammation

Granulomatous Reaction and Formation

Tuberculous Granuloma

Other particle induced granulomas

Granulomas of Unknown origin
Granulomatous Inflammation

• A – Langhans type giant cell surrounded by epitheloid giant cells
• B – granulomas with Langhans-type giant cells centrally, a surrounding lymphocytic infiltrate. Tuberculous meningitis.
• C - Numerous uniform, round granulomas within a lymph node in sarcoidosis
Granulomatous Reaction and Formation

<table>
<thead>
<tr>
<th>Cause</th>
<th>Example</th>
</tr>
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<td>Specific infections</td>
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<td>Crohn's disease</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Wegener's granulomatosis</td>
</tr>
</tbody>
</table>
Sarcoidosis

• Systemic granulomatous disease
  – unknown cause – likely genetic predisposition with environmental trigger
  – affects young and middle-aged adults
  – African-Americans more frequently affected, more severe disease

• Bilateral hilar lymphadenopathy, pulmonary infiltrates, and ocular and skin lesions.

• Heart, liver, spleen, salivary glands, muscles, bones, kidneys, and central nervous system

• Otolaryngologic manifestations
  – 10-15% of patients
  – Cervical adenopathy – high yield with FNA
  – Parotid involvement
  – Sinonasal manifestations
Sarcoidosis

• Diagnosis –
  – clinicoradiologic findings
  – histologic evidence of noncaseating epithelioid granulomas
  – exclusion of other granulomatous diseases.

• Prognosis - correlates with mode of onset, host characteristics, initial clinical course, and extent of disease.
Sarcoidosis

• Management – optimal treatment has not been well defined.
  – Corticosteroids - mainstay of treatment, but little evidence for the optimal initiation, dosage, or duration of therapy.
  – Cytotoxic agents and immunomodulators - reserved for treatment of complex or refractory disease.
    • methotrexate
    • antimalarial agents are used frequently for skin lesions, limited success in the treatment of pulmonary disease.
    • Lung and cardiac transplantation is reserved for end-stage disease.
Metal Induced Granuloma

*Berylliosis*

Chest Radiographs

Bilateral hilar adenopathy and fine nodular upper lobe infiltrates in CBD
Metal Induced Granuloma

Berylliosis

Typical trans-bronchial biopsy in CBD

Epithelioid granuloma
Multinucleated Giant cell
Schumann body
Lymphocytic infiltrates
Metal Induced Granuloma

Berylliosis

Skin lesions in < 5%
Metal Induced Granuloma

Berylliosis

Accumulation of Be specific cells in the BAL fluid

Metal Induced Granuloma

Berylliosis

Patients with CBD have higher BAL Beryllium Specific Proliferation

Proliferation Results

Stimulation Index

Controls  BH  BHWCD  CBD

Patient Groups

* = p < 0.05

3/8/2005
Beryllium is recognized as a specific antigen by lung T-cells of CBD patients.
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Beryllium is presented to Be-specific T-cells in the context of HLA-class II molecules.

Saltini C et al NEJM 1989

Immunochemistry and Immunogenetics of CBD (2) (Milestones)
Beryllium is recognized as a specific antigen by lung T-cells of CBD patients.

Beryllium is presented to Be-specific T-cells in the context of HLA-class II molecules.

A glutamate in position 69 of the HLA-DP β-chain has been associated with susceptibility to CBD.

Richeldi L. et al. Science 1993
Beryllium is recognized as a specific antigen by lung T-cells of berylliosis patients.

Beryllium is presented as a specific antigen to Be-specific T-cell in the context of HLA-class II molecules.

A glutamate in position 69 of the HLA-DP β-chain has been associated with susceptibility to CBD.

The HLA-DPGlu69 supratypic marker has been found in 62-97% of CBD and beryllium hypersensitivity subjects in different study populations.

<table>
<thead>
<tr>
<th>Study</th>
<th>HLA-DPGlu69 phenotype frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richeldi 1993</td>
<td>97%</td>
</tr>
<tr>
<td>Richeldi 1997</td>
<td>83%</td>
</tr>
<tr>
<td>Wang 1999; 2001</td>
<td>97%</td>
</tr>
<tr>
<td>Saltini 2001</td>
<td>76%</td>
</tr>
<tr>
<td>Rossman 2002</td>
<td>84%</td>
</tr>
<tr>
<td>Mayer 2003</td>
<td>83%</td>
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<tr>
<td>McCanlies 2004</td>
<td>82%</td>
</tr>
<tr>
<td>Gaede 2005</td>
<td>62%</td>
</tr>
<tr>
<td>Amicosante 2005</td>
<td>81%</td>
</tr>
</tbody>
</table>
HLA-DPGlu69 is playing a functional role in beryllium presentation:

1. Anti-HLA-DP monoclonal antibody block the T-cell response to beryllium

Amicosante et al. Eur Respir J 2002
HLA-DPGlu69 is playing a functional role in beryllium presentation:

1. Anti-HLA-DP monoclonal antibody block the T-cell response to beryllium

2. Beryllium presentation to Be-specific lung T-cell lines is restricted by HLA-DPGlu69 carrying MHC alleles
HLA-DPGlu69 is playing a functional role in beryllium presentation:

1. Anti-HLA-DP monoclonal antibody block the T-cell response to beryllium

2. Beryllium presentation to Be-specific lung T-cell lines is restricted by HLA-DPGlu69 carrying MHC alleles

3. Only HLA-DPGlu69-positive alleles are able to present beryllium to Be-specific T-cells clones
