UNIVERSITY OF DUNDEE

Hypersensitivity and the lung

Sara Marshall, Professor of Clinical Immunology
Phase 2 2010-2011: Respiratory Medicine

Objectives

- Apply knowledge about immunological disease mechanisms to the lung
  - Classify common respiratory diseases according to the Gel and Coombs classification of hypersensitivity
  - Use this to inform understanding of disease investigation and treatment

Hypersensitivity reactions

- Definition
  - Immune response that results in bystander damage to the self
- Usually exaggeration of normal immune mechanisms
- Pathophysiological basis for many diseases, including allergy and autoimmunity

Overlap slide from Haematology lecture 3

Classification of hypersensitivity reactions

- **Gel and Coomb's classification**
  - Type I: Immediate hypersensitivity
  - Type II: Direct cell killing
  - Type III: Immune complex mediated
  - Type IV: Delayed type hypersensitivity

Useful way to think about disease pathogenesis, but many conditions are a mixture of different types of reactions (so things are not always so simple ...)

Please provide an example of Type 1 hypersensitivity in the lung...

OBSTRUCTIVE AIRWAY DISEASE Terminology

- Early onset / late onset
- Atopic / non-atopic
- Extrinsic / Intrinsic

Recognise the slides? See Prof Lipworth's introductory lecture on obstructive airways disease

THE INFLAMMATORY CASCADE

Genetic predisposition + Trigger factor • **Avoidance**
(e.g. viral, allergen, chemicals)

↓

Airway inflammation • Anti-inflammatory - corticosteroid

↓

Mediators
(e.g. histamine, leukotriene) • Anti-leukotriene & Antihistamine

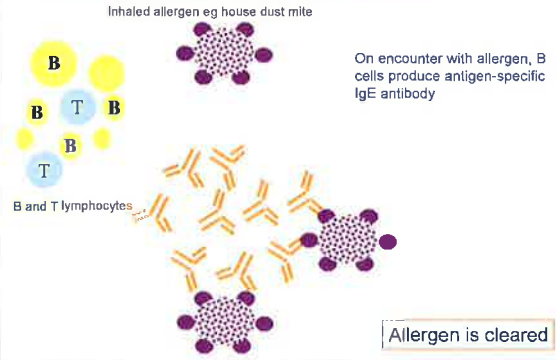
↓

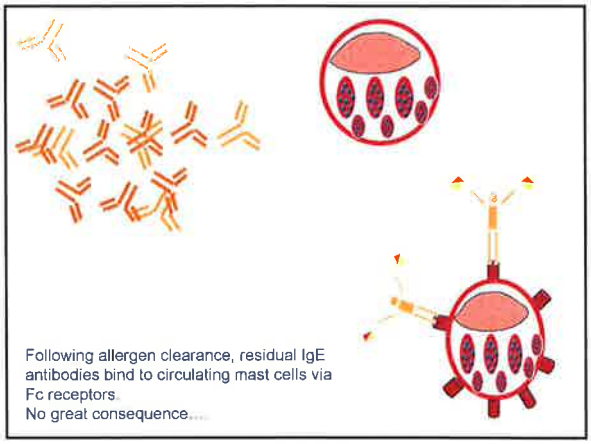
Twitchy smooth muscle
(Hyper-reactivity) Bronchodilators - B2-agonists

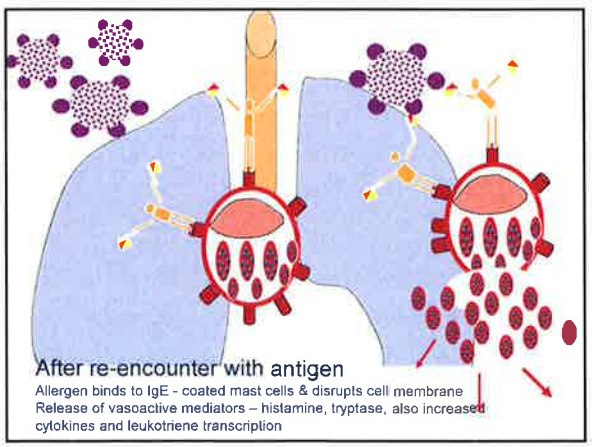
Classification of asthma

- Extrinsic asthma
  - Response to external allergen
  - IgE mediated
  - Triggers: house dust mite, grass pollen, animal dander, etc
  - Associated with other allergic disease
- Intrinsic asthma
  - Result of lowering of threshold for mast cell degranulation
  - Not IgE mediated
  - Triggers: cold, exercise, NSAIDs
  - Can be associated with other allergic disease too!

Pathophysiology of extrinsic asthma







What happens clinically when this reaction occurs in the lung?

- Release of histamine and other inflammatory mediators
  - Muscle spasm
    - Causes bronchoconstriction
      - Clinical manifestation: wheeze
  - Mucosal inflammation
    - Causes mucosal oedema and increases secretions
      - Clinical manifestation: sputum production
  - Inflammatory cell infiltrate
    - Infiltration of lymphocytes and eosinophils into bronchioles
      - Clinical manifestation: sputum often yellow
      - Associated with chronicity

What about intrinsic asthma?

- Intrinsic asthma
  - Usually (but not always) results from lowering of threshold for mast cell degranulation
  - Not IgE mediated
  - Triggers: cold, exercise, NSAIDs
  - Can be associated with other allergic disease too!

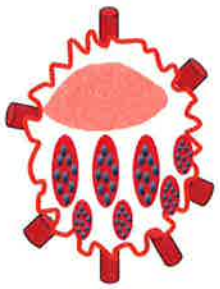
What about intrinsic asthma?

Two types of intrinsic asthma

- Directly triggered bronchoconstriction
  - Direct response of bronchiole smooth muscle to stimulus
    - Smoke
    - Volatile chemicals
    - Viral infection
    - Cold air
- Histamine mediated
  - Non-IgE mediated mast cell degranulation causes histamine release
    - NSAIDs
    - Radiocontrast medium
    - Viral infection
    - Exercise

What's happening in intrinsic asthma?

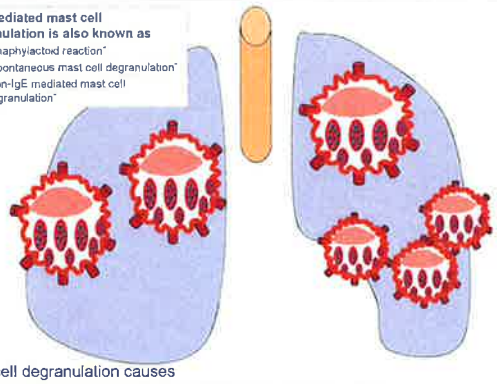
- Change in threshold for mast cell degranulation
- Change in membrane stability
- Displacement of histamine from vesicles



"Twitchy" mast cells

Not IgE mediated mast cell degranulation is also known as

- "Anaphylactoid reaction"
- "Spontaneous mast cell degranulation"
- "non-IgE mediated mast cell degranulation"



Mast cell degranulation causes
Release of vasoactive mediators – histamine, tryptase, also increased cytokines and leukotriene transcription etc

Conditions associated with non-IgE mediated mast cell degranulation

- Localised to lung
  - Cold air or change in air temperature
  - Exercise
  - Viral infections
- May also occur as part of systemic condition
  - Drugs
  - Thyroid disease
  - Systemic mastocytosis
  - Infection

Key clinical sign of non-IgE mediated mast cell degranulation

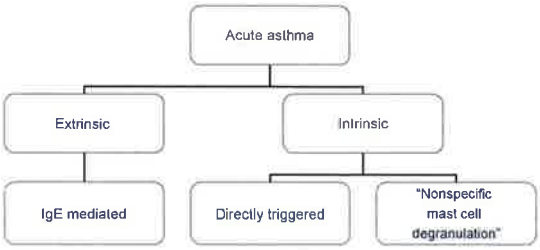
Conditions associated with non-IgE mediated mast cell degranulation

- Localised to lung
- May also occur as part of systemic condition
  - Drugs

Aspirin induced asthma

- Aspirin induced asthma is common
  - affects ~20% of asthmatics
  - Characterised by wheeze 0.5-3 hours after ingestion
  - Triggered by aspirin and also other classical NSAIDS (particularly diclofenac, ibuprofen)
  - Paracetamol and COX-2 inhibitors (eg celecoxib) generally OK
- Samter's triad
  - Affects 2-3% asthmatics
  - asthma, nasal polyps and salicylate sensitivity
  - severe end of the aspirin sensitive spectrum
  - May require dietary modification because of high prevalence of salicylates in some foods

Classification of asthma



How does this help your patient with asthma?

- Identify their triggers
  - Clinical history
    - Ask about context of asthma episodes
    - Ask about other allergic reactions Don't forget to ask about medication
  - Specific IgE tests
  - Skin prick tests
  - Response to histamine challenge

→ Targeted avoidance

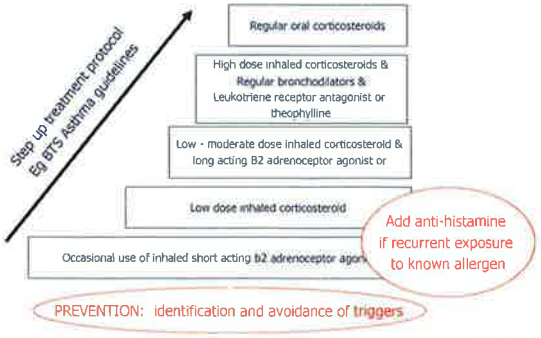
How does this help your patient with asthma?

- Management
  - If mast cell degranulation is implicated, target the mast cell!
    - Antihistamines
      - As required
      - Prophylactic
        - » NB – antihistamines are much more effective if taken early in the course of a reaction
    - Leukotriene receptor antagonists
      - Prevent synthesis of other mast cell mediators
      - Often useful in aspirin-sensitive individuals
    - Mast cell stabiliser
      - eg cromoglycate in exercise-induced asthma, especially kids
    - Corticosteroids
      - Anti-inflammatory effect

How does this help your patient?

- Think holistically: Are allergies affecting other organ systems being appropriately managed?
  - Eg severe food allergies can cause acute asthmatic attack or anaphylaxis
  - Severe or poorly controlled asthma is a major risk factor for fatal anaphylaxis in individuals with severe food allergy

How does this help you look after your patients?

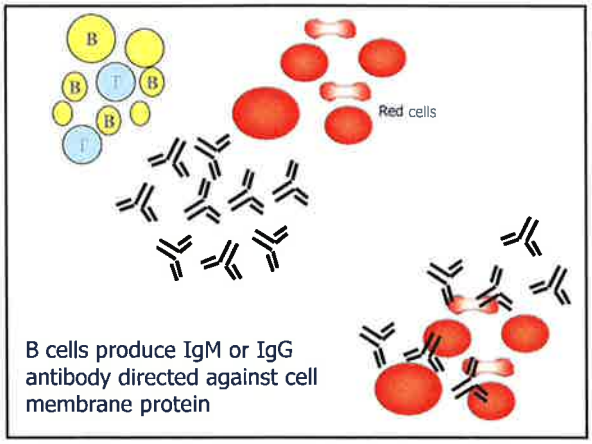


Classification of hypersensitivity reactions

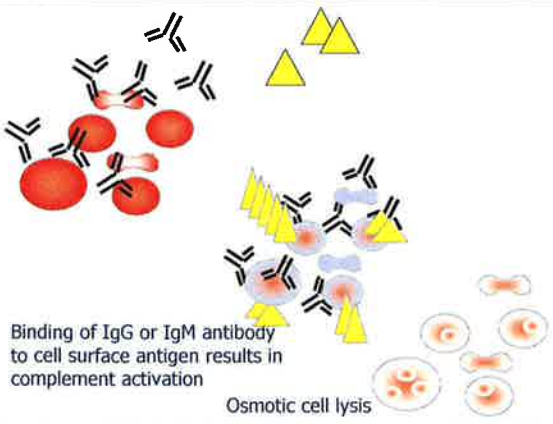
- Gel and Coomb's classification
  - Type I: Immediate hypersensitivity
  - Type II: Direct cell killing
  - Type III: Immune complex mediated
  - Type IV: Delayed type hypersensitivity

Type II Hypersensitivity: Direct cell killing

- Key features
  - Antibody to cell surface antigens
- Pathophysiology
  - Antibody binds to cell-surface antigen
  - Results in:
    - Activation of complement
      - cell lysis
      - opsonisation
    - Antibody-mediated phagocytosis

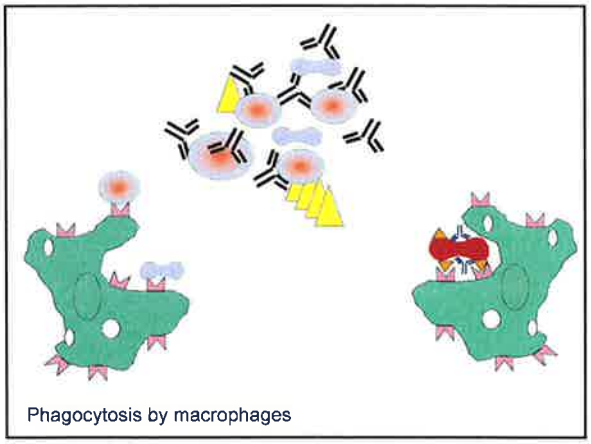


B cells produce IgM or IgG antibody directed against cell membrane protein



Binding of IgG or IgM antibody to cell surface antigen results in complement activation

Osmotic cell lysis



Phagocytosis by macrophages

Type II Hypersensitivity: Clinical examples

- Blood cells
  - Autoimmune haemolytic anaemia
  - Idiopathic thrombocytopaenic purpura
  - ABO transfusion reactions
- Kidney
  - Goodpasture's syndrome (antibodies to glomerular basement membrane)
- Nervous system
  - Myasthenia gravis (antibodies to acetyl choline receptor)
- Endocrine system
  - Graves' disease (antibodies to TSH receptor)
- Skin
  - Pemphigus vulgaris (antibodies to epithelial cell cement)

Type II Hypersensitivity in the lung?

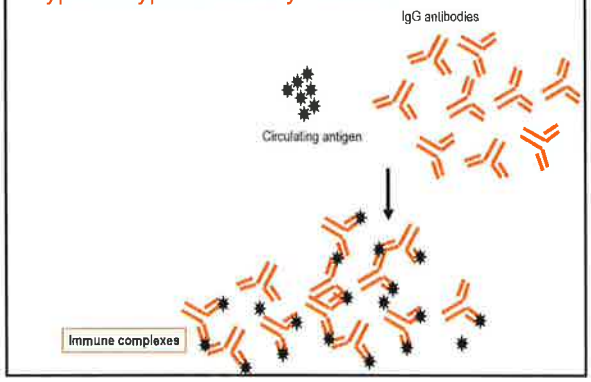
- Blood cells
  - Autoimmune haemolytic anaemia
  - Idiopathic thrombocytopaenic purpura
  - ABO transfusion reactions
- Kidney and Lung
  - Goodpasture's syndrome (antibodies to glomerular basement membrane cross react with alveolar basement membrane)
- Nervous system
  - Myasthenia gravis (antibodies to acetyl choline receptor)
- Endocrine system
  - Graves' disease (antibodies to TSH recep
- Skin
  - Pemphigus vulgaris (antibodies to epithelia

But this is small print; here for completeness

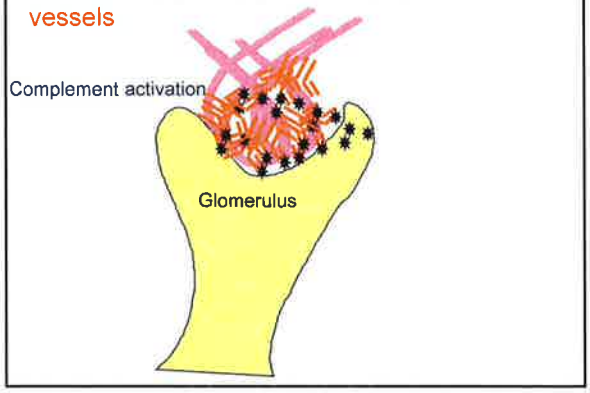
Classification of hypersensitivity reactions

- Gel and Coomb's classification
  - Type I: Immediate hypersensitivity
  - Type II: Direct cell killing
  - Type III: Immune complex mediated
  - Type IV: Delayed type hypersensitivity

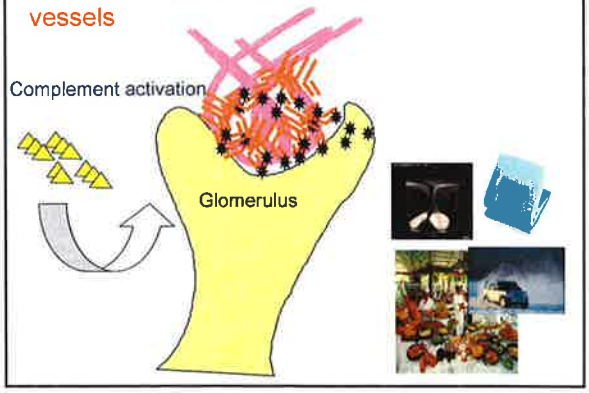
Type III hypersensitivity reaction



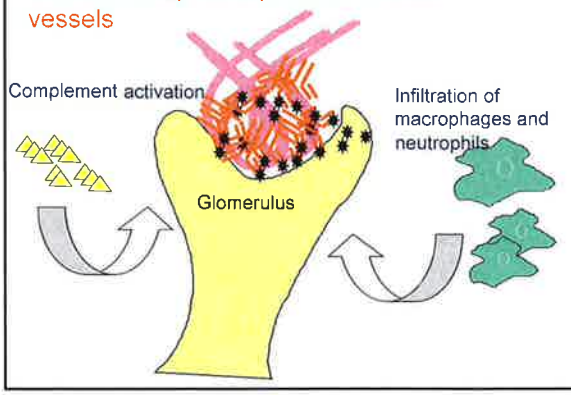
Immune complex deposition in small vessels



Immune complex deposition in small vessels



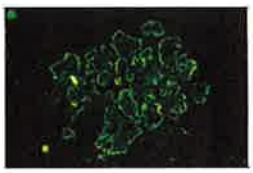
Immune complex deposition in small vessels



Immune complex deposition results in small vessel vasculitis

Systemic antigen causes systemic disease
- –fever
- –renal impairment
- –vasculitic skin rash
- –arthralgias

Immune complex deposition in joints causes arthralgia



Deposition of IgG immune complexes in glomeruli causes renal dysfuntion

Immune complex deposition in skin causes vasculitic purpura

Please provide an example of Type III hypersensitivity in the lung...

– Type III: Immune complex mediated

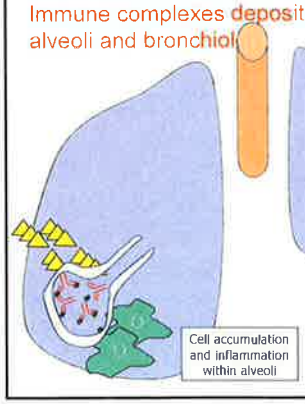
Causes of hypersensitivity pneumonitis

Disorder	Source	Organism/agent
Farmer's Lung	Mouldy hay, straw, grain	*Aspergillus fumigatus Micropolyspora faeni*
Bird fancier's lung	Avian excreta, feathers	Avian serum proteins
Malt worker's lung	Mouldy maltings	*Aspergillus clavatus*
Cheese worker's lung	Mouldy cheese	*Aseprgillus clavatus Penicillum casei*
Maple bark stripper's lung	Bark from stored maple	*Cryptostroma corticale*

Farmer's lung – acute disease

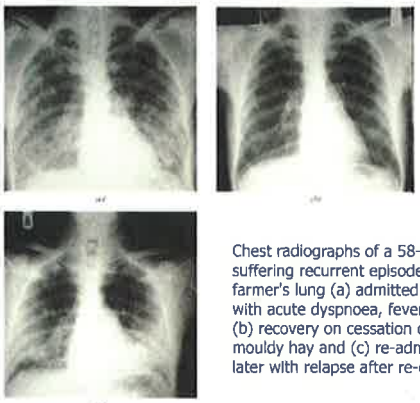
- Repeated inhalation of fungal particles stimulates IgG antibody formation
- Subsequent exposure results in formation of immune complexes between antibody and antigen
- Results in complement activation.... Inflammation.... Recruitment of other cells.....

Acute hypersensitivity pneumonitis: Immune complexes deposited in the walls of alveoli and bronchioles



Causes wheezing and malaise after 4-8 hours after exposure to antigen.
May be associated with dry cough, pyrexia, breathlessness
Examination often normal
= acute hypersensitivity pneumonitis

When you are revising, this may seem confusing. Remember that ACUTE hypersensitivity pneumonitis is mediated by Type III hypersensitivity response. Chronic hypersensitivity pneumonitis is different – read on....



Chest radiographs of a 58-year-old man suffering recurrent episodes of acute farmer's lung (a) admitted to hospital with acute dyspnoea, fever, hypoxaemia, (b) recovery on cessation of contact with mouldy hay and (c) re-admitted 4 months later with relapse after re-exposure.

Imaging 15:23-30 (2003)

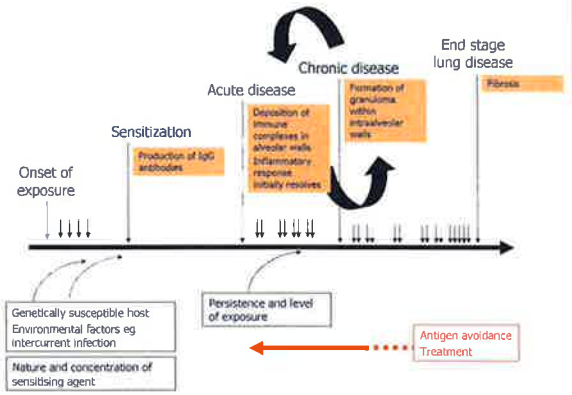
Chronic hypersensitivity pneumonitis

- Repeated episodes of inflammation results in persistent stimulation of phagocytes
- Activation of T cells also occurs, with formation of non-caseating granuloma in alveolar walls (i.e. type IV hypersensitivity reaction)
- Finally causes fibrosis of lung tissue

Chronic hypersensitivity pneumonitis

- Chronic breathlessness
- Hypoxia
- Pulmonary hypertension
- Eventually end stage lung disease

NB CHRONIC hypersensitivity pneumonitis is a combination of Type IV hypersensitivity response and fibrotic change in response to chronic damage



Lung damage in hypersensitivity pneumonitis

Acute	Early chronic ("subacute")	Established chronic
In early hypersensitivity pneumonitis, High resolution CT may show transient, subtle, diffuse infiltrate during acute disease, but is normal between episodes		
	➢ High resolution CT scan in early chronic hypersensitivity pneumonitis ➢ Bilateral, diffuse distribution of centrilobular nodules of ground-glass opacity ➢ Reflects the presence of peribronchiolar inflammation	➢ High resolution CT scan in established chronic hypersensitivity pneumonitis ➢ Note areas of tissue destruction and fibrosis ➢ Eventually becomes "honeycomb lung"

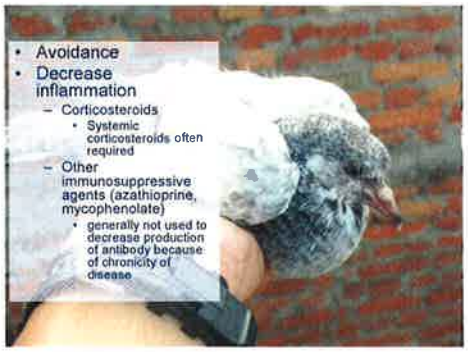
Explain the clinical features of acute hypersensitivity pneumonitis

Wheeze	
Breathlessness	
Malaise, pyrexia	

What investigations would you do?

Acute hypersensitivity pneumonitis	
Chronic hypersensitivity pneumonitis	

Management of hypersensitivity pneumonitis



What's in a name?

"Hypersensitivity pneumonitis" and "Extrinsic Allergic Alveolitis" are used interchangeably, but one is a better name than the other.
Which one?

Hypersensitivity pneumonitis

Extrinsic allergic alveolitis

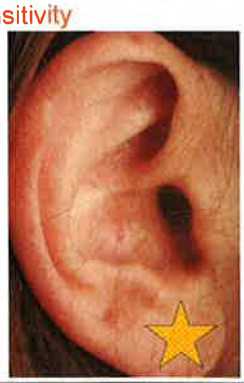
Gel and Coombs classification

- Type I: Immediate hypersensitivity
- Type II: Direct cell killing
- Type III: Immune complex mediated
- Type IV: Delayed type hypersensitivity

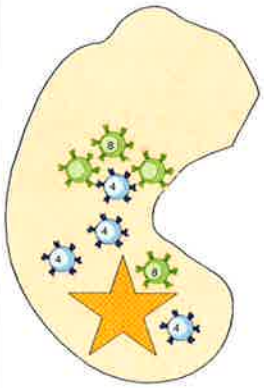
Type IV hypersensitivity: Delayed type hypersensitivity

- T cell mediated hypersensitivity
- Pathophysiology
  - Initial sensitisation to antigen
    - generation of "primed" T cells
  - Subsequent exposure
    - activation of previously primed T cells
    - Recruitment of macrophages, other lymphocytes, neutrophils
    - Release of proteolytic enzymes, persistent inflammation

Type IV hypersensitivity: delayed type hypersensitivity

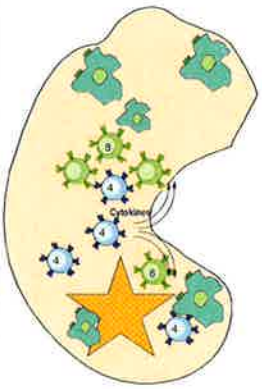


Type IV Hypersensitivity



- Infiltration of activated T cells

Type IV Hypersensitivity



- Infiltration of activated T cells
- Recruitment of macrophages
- If fails to clear stimulus, results in formation of granuloma

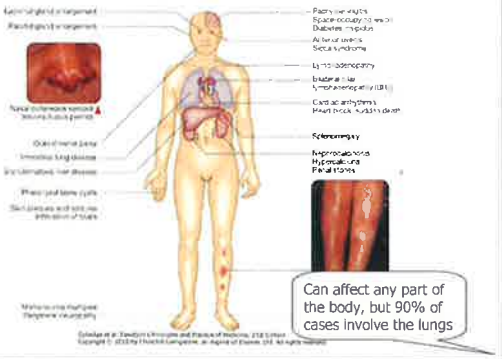
Examples of Type IV hypersensitivity responses in the lung

- Sarcoidosis
- Tuberculosis
- Chronic stage of hypersensitivity pneumonitis
- Acute cellular rejection of transplanted lung

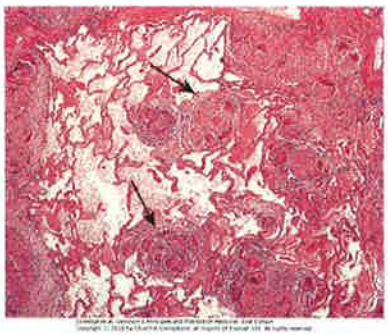
Sarcoidosis

- Multisystem granulomatous disease
- Unknown aetiology
- Characterised by presence of granulomas
- Underlying pathophysiology is type IV delayed type hypersensitivity response to unknown antigen

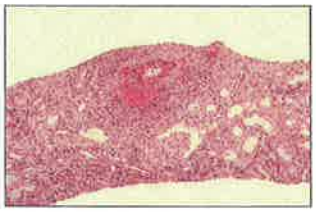
Sarcoid is a multisystem disorder



...characterised by granuloma

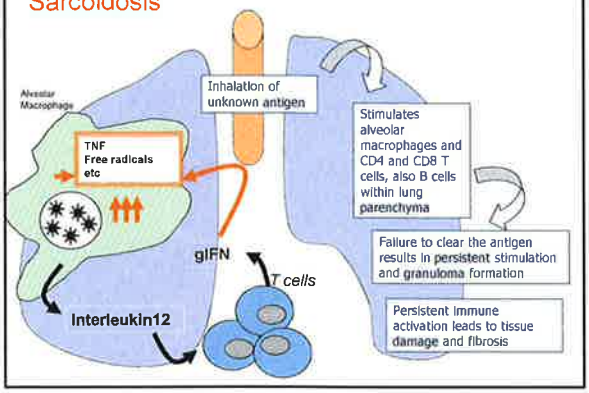


So what's a granuloma?



- Granuloma consists of organised collection of activated macrophages and lymphocytes
- Granuloma formation
  - non-specific inflammatory response triggered by diverse antigenic agents or by inert foreign materials
  - Initiated by activation of T lymphocytes and macrophages, and mediated by an array of different cytokines

Sarcoidosis

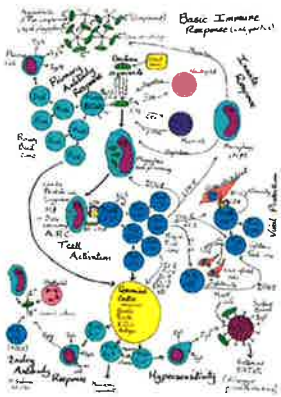


Management of sarcoid

- Watchful waiting
  - many patients undergo spontaneous remission
- NSAIDS
  - For acute onset of disease
- Systemic corticosteroids
  - Block T cell activation
  - Block macrophage activation

Diseases characterised by type IV hypersensitivity and granuloma formation

- Sarcoidosis
- Tuberculosis
- Leprosy (some forms)
- Berylliosis, silicosis and other dust diseases
- Chronic stage of hypersensitivity pneumonitis
- Crohn's disease



s.e.marshall@dundee.ac.uk