Rheumatic Heart Disease

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Consultant Immunology

Objectives

- To understand the basis of rheumatic fever as an immunologically mediated late complication of Streptococcal infection
- To know that autoimmunity results from production of cross reacting antibodies against Streptococcal antigens
- To describe Rheumatic heart disease as one of the several manifestations of rheumatic fever
- To know the signs, symptoms, pathogenesis, treatment and prophylaxis of rheumatic heart disease

Rheumatic Fever

- Epidemiology of Rheumatic Fever (RF)

- 3% of persons with untreated group **A streptococcal pharyngitis** develop rheumatic fever

- 15-20 million new cases a year in developing countries

- **Risk factors**
  - Low standard of living
  - Crowding

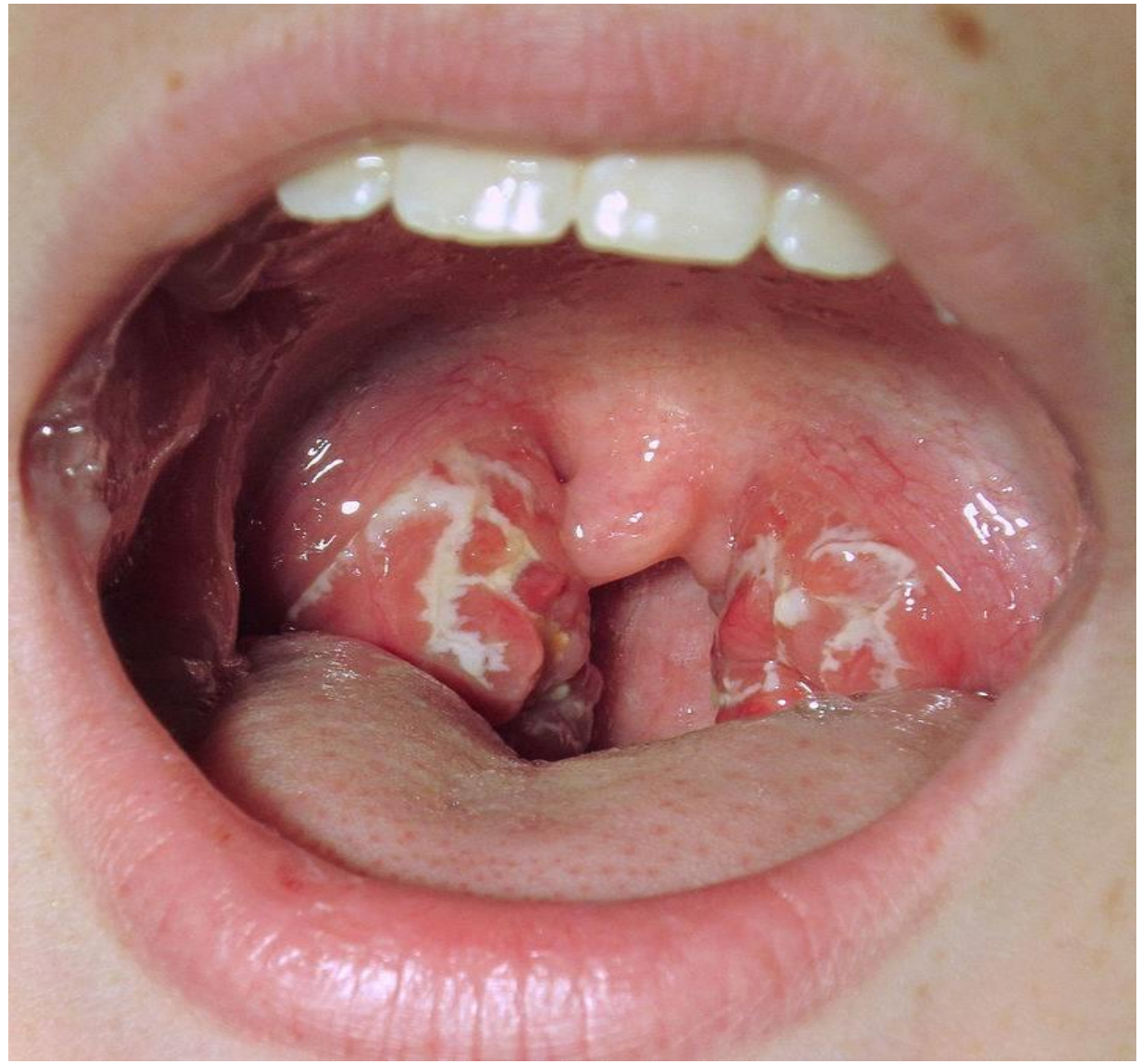
Rheumatic Fever

- Some genetic factors increase the susceptibility to autoimmune reactions in RHD.
- MHC class II allele **DR7** is associated with RHD, and its combination with certain DQ alleles is seemingly associated with the development of valvular lesions.
- Antigen-presenting cells bearing the **DR7** molecule from RHD patients preferentially recognize heart-tissue protein

  (Guilherme L, Kalil J. Ann N Y Acd Sci 2007,1107:426-433)

Rheumatic Fever

- Is an inflammatory disease that can involve the heart, joints, skin, and brain.
- Develop a **Group A Streptococcal infection** such as:
- Strep. throat infection or scarlet fever
- The disease develops 2 to 4 weeks after a throat infection
- commonly appears in children ages 5-15



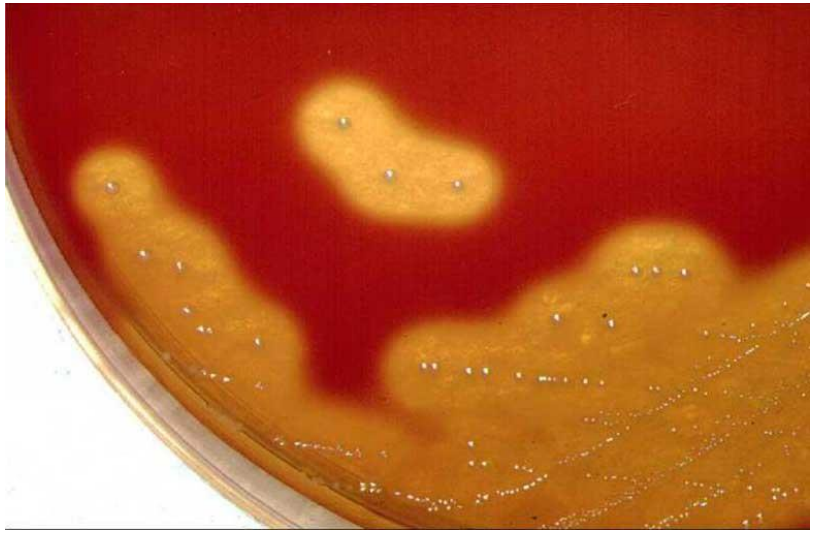
Rheumatic Fever

- Caused by **group A streptococcus**

- There is a latent period of 3 weeks (1–5 weeks) between the group A streptococcal infection and the appearance of the clinical features of RF

Group A β–haemolytic streptococcus

- All cases associated with recent infection (e.g. pharyngitis)
- Antibody and cellular immune response cross-reacts with human connective tissue



A streptococcus pyogenes

- Group A streptococcus pyogenes has a cell wall composed of branched polymers which sometimes contain "***M proteins*** " that are highly antigenic

- The antibodies which the immune system generates against the "*M proteins*" may cross react with cardiac myofiber protein myosin and smooth muscle cells of arteries, inducing cytokine release and tissue destruction

- This inflammation occurs through direct attachment of complement and Fc receptor-mediated recruitment of neutrophils and macrophages

Group A β–haemolytic streptococcus

- M proteins :Adherence of Streptococcus pyogenes to host cells & inhibiting the host immune response
- Hyaluronic acid capsule: Camouflages the bacterium
- Streptokinases: Dissolve blood clots
- Peptidases: Degrades proteins involved in immune response
- Pyrogenic toxins: Stimulate fever, rash & shock
- Streptolysins: Lyse erythrocytes, leukocytes & platelets

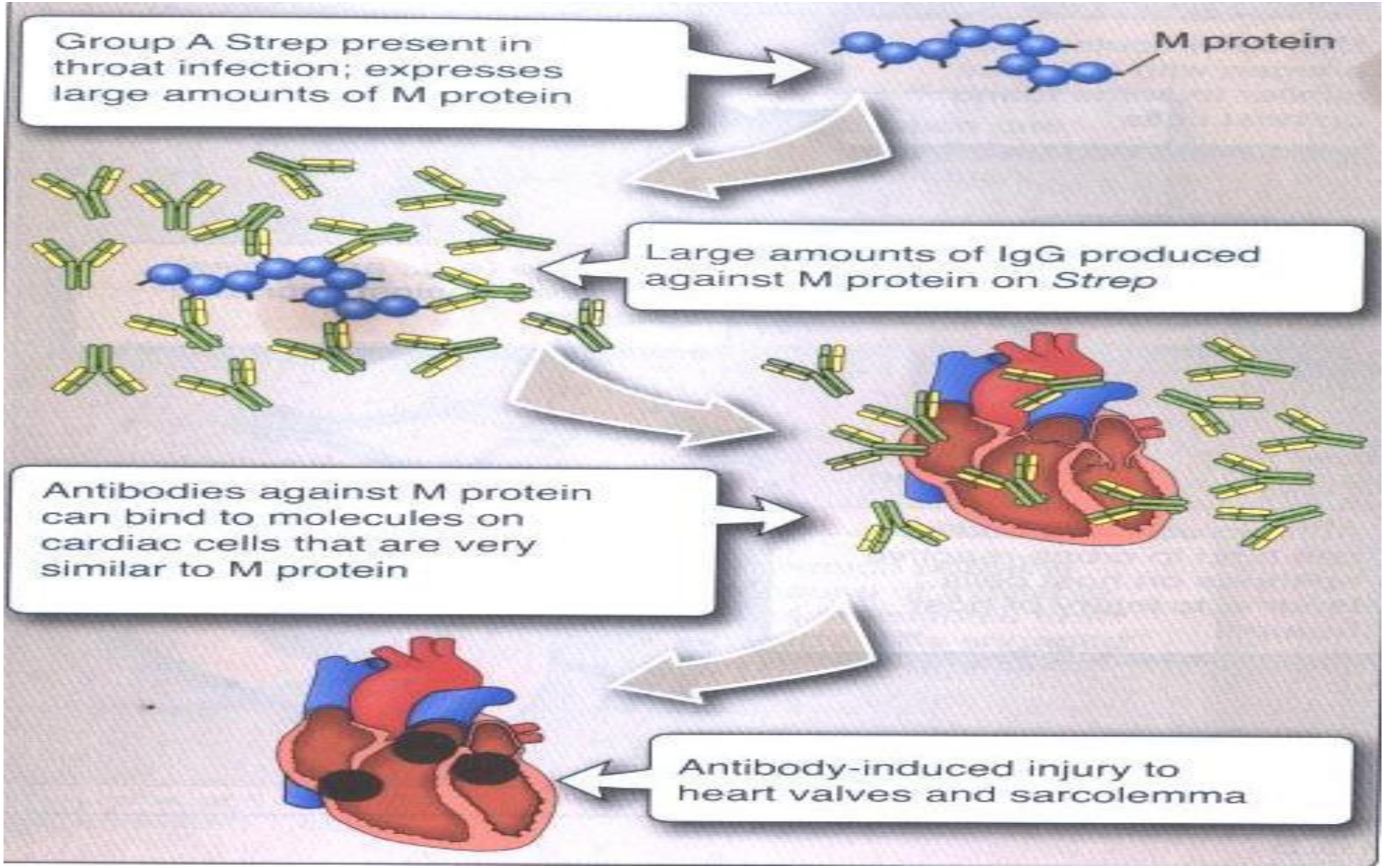
PATHOGENESIS

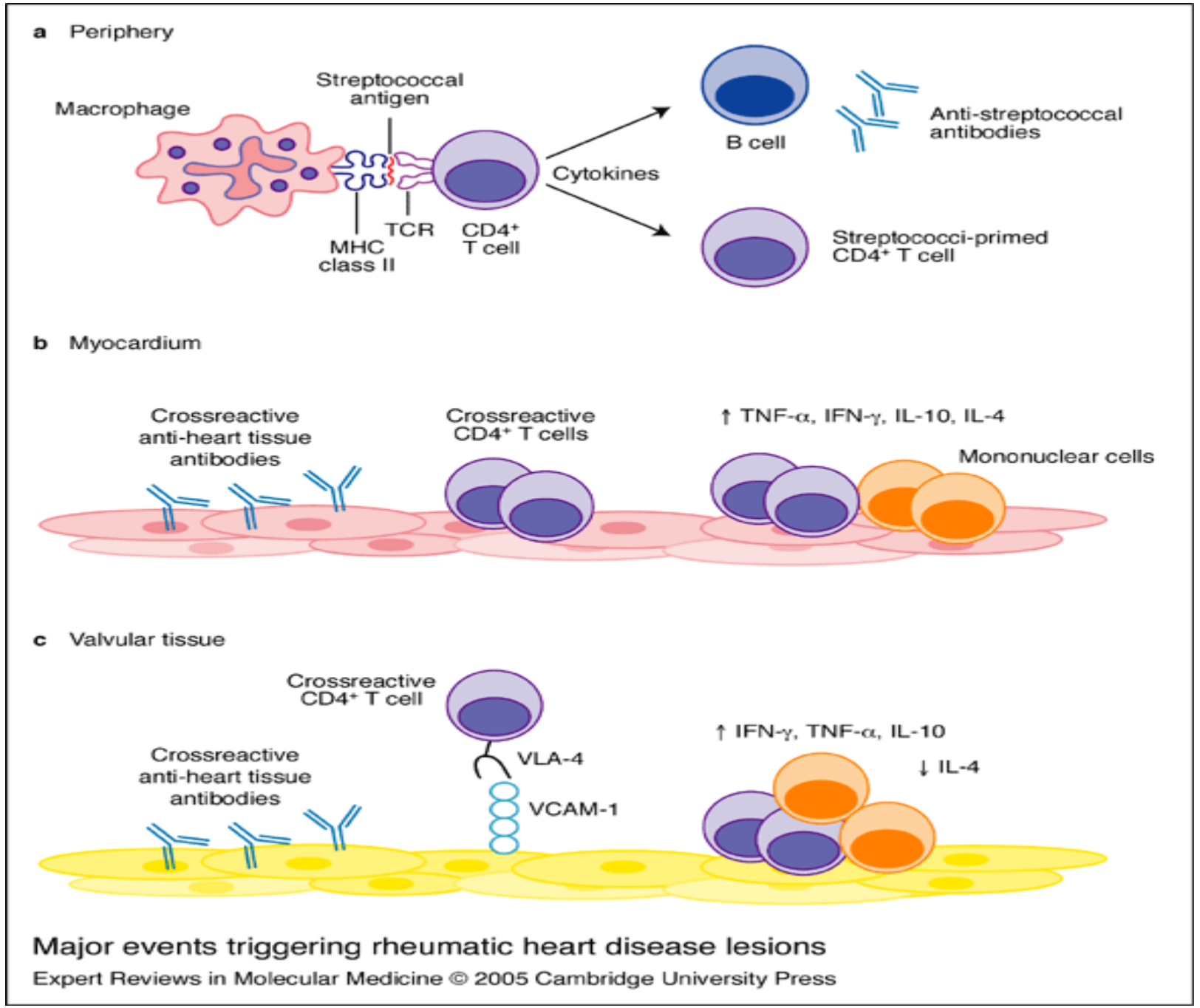
- Rheumatic fever affect the peri-arteriolar connective tissue
- It is believed to be caused by antibody cross-reactivity
- This cross-reactivity is a Type II hypersensitivity reaction and is termed *molecular mimicry*

Pathogensis

- **Type II hypersensitivity**
- the **antibodies** produced by the immune response bind to **antigens** on the patient's own cell surfaces.

- These cells are recognized by **macrophages** or **dendritic cells**, which act as antigen-presenting cells. This causes a **B cell** response, wherein antibodies are produced against the foreign antigen


Group A Strep present in throat infection; expresses large amounts of M protein
M protein
Large amounts of IgG produced against M protein on *Strep*
Antibodies against M protein can bind to molecules on cardiac cells that are very similar to M protein
Antibody-induced injury to heart valves and sarcolemma



Major events triggering rheumatic heart disease lesions

Diagram illustrating the two hit theory of rheumatic heart disease.

Group A streptococcal infection leads to the production of anti-group A carbohydrate antibody which cross-reacts with the valve endothelium as well as with the myocardium and up-regulates vascular cell adhesion molecule-1 (VCAM-1) on the valve endothelium.

T cells adhere to the VCAM-1 on valve endothelium and extravasate into the valve

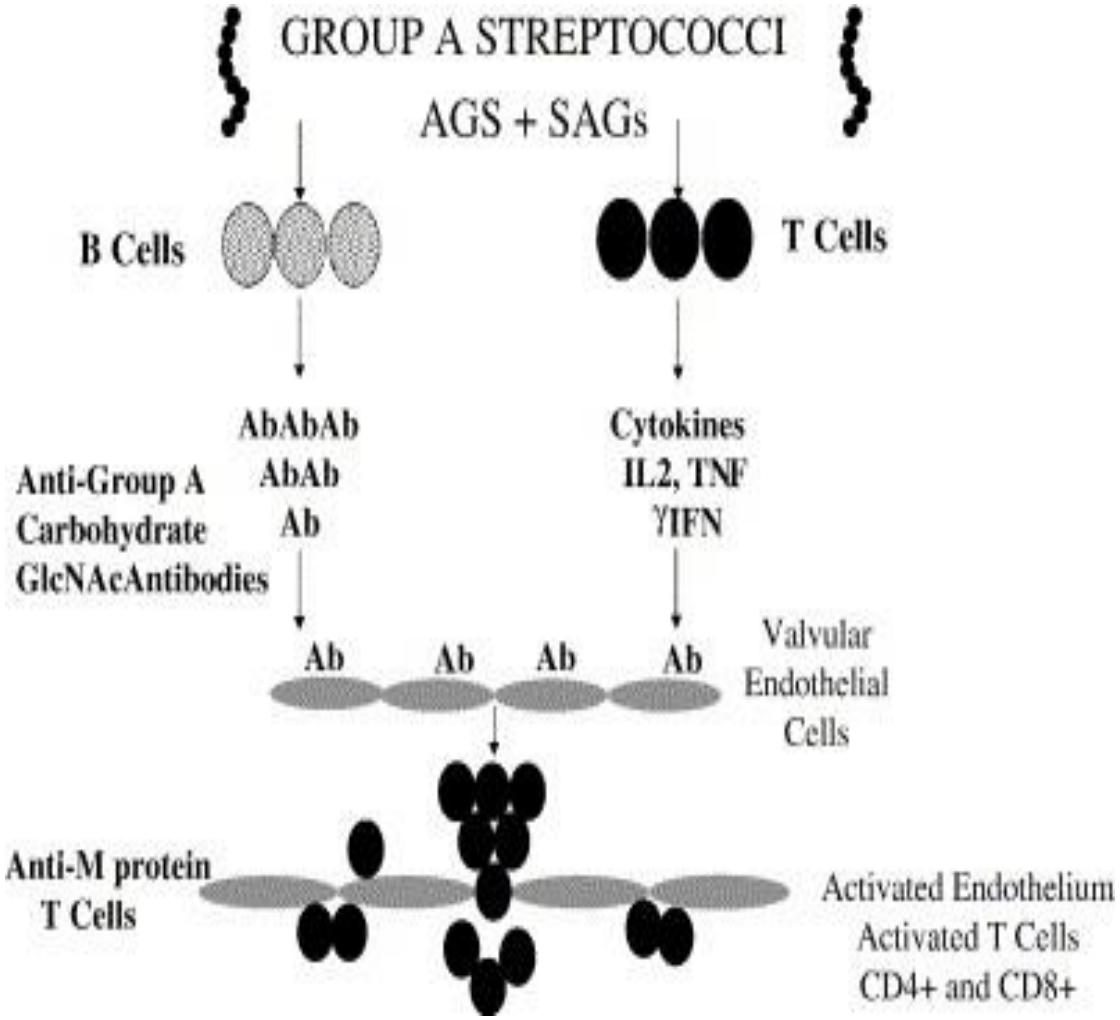
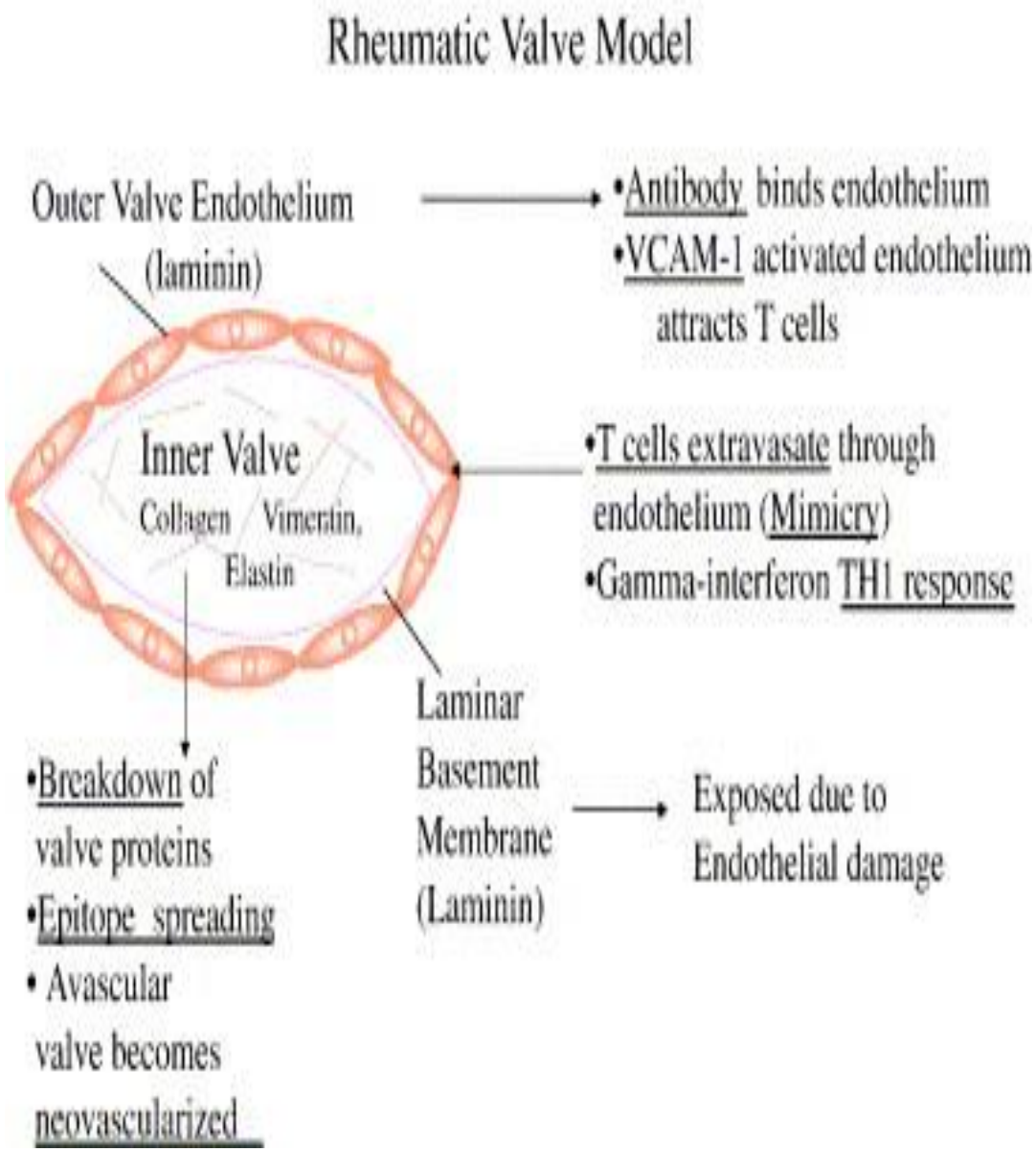


Diagram illustrating the process of initial mimicry which leads to

granuloma formation, gamma interferon production and scarring in the valve.

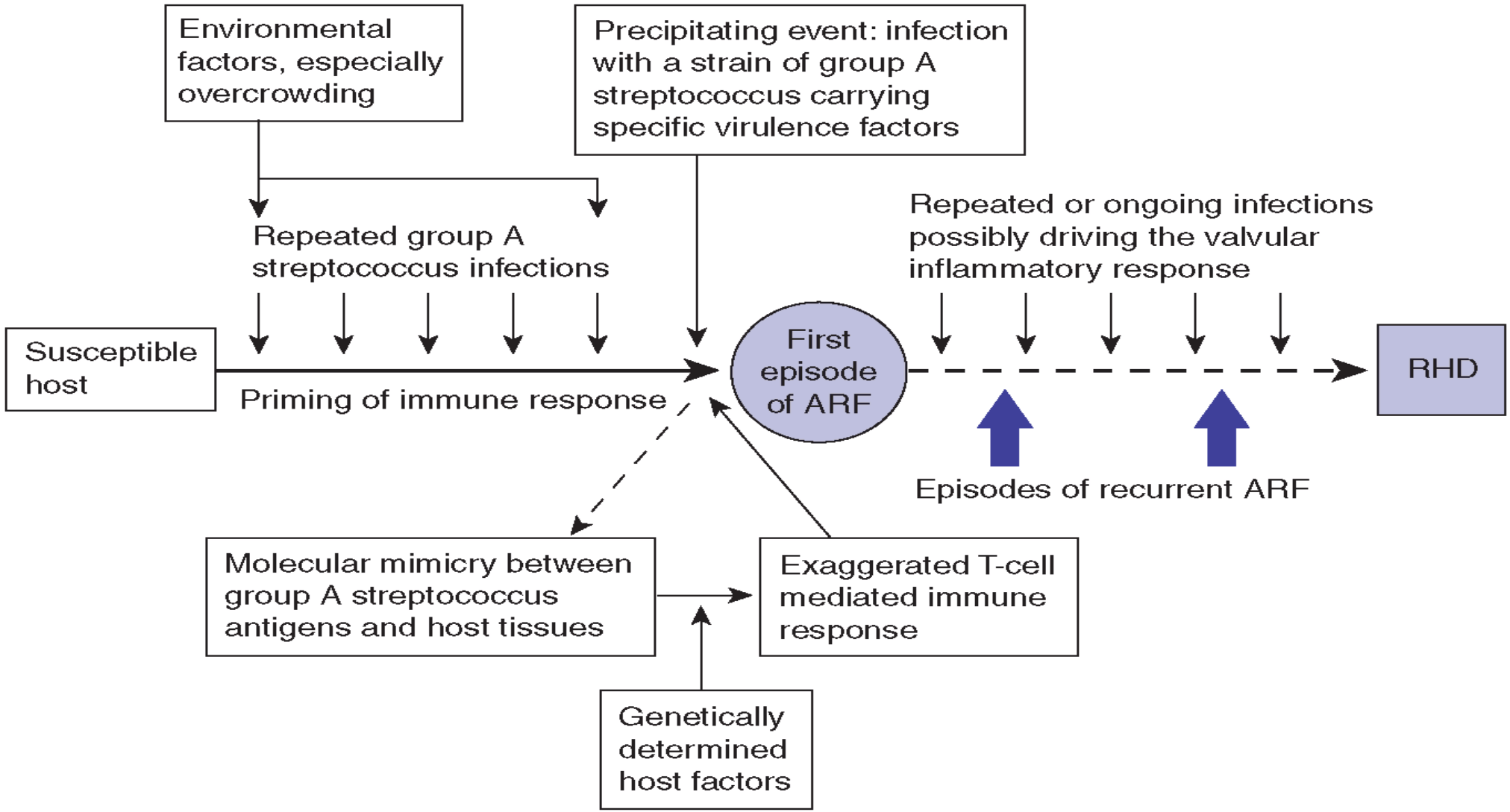
After the initial process has developed inflammation in the valve,

other proteins in the valve may then be recognized by the immune system leading potentially to epitope spreading and responses against other valve proteins such as vimentin and collagen.



Pathophysiology

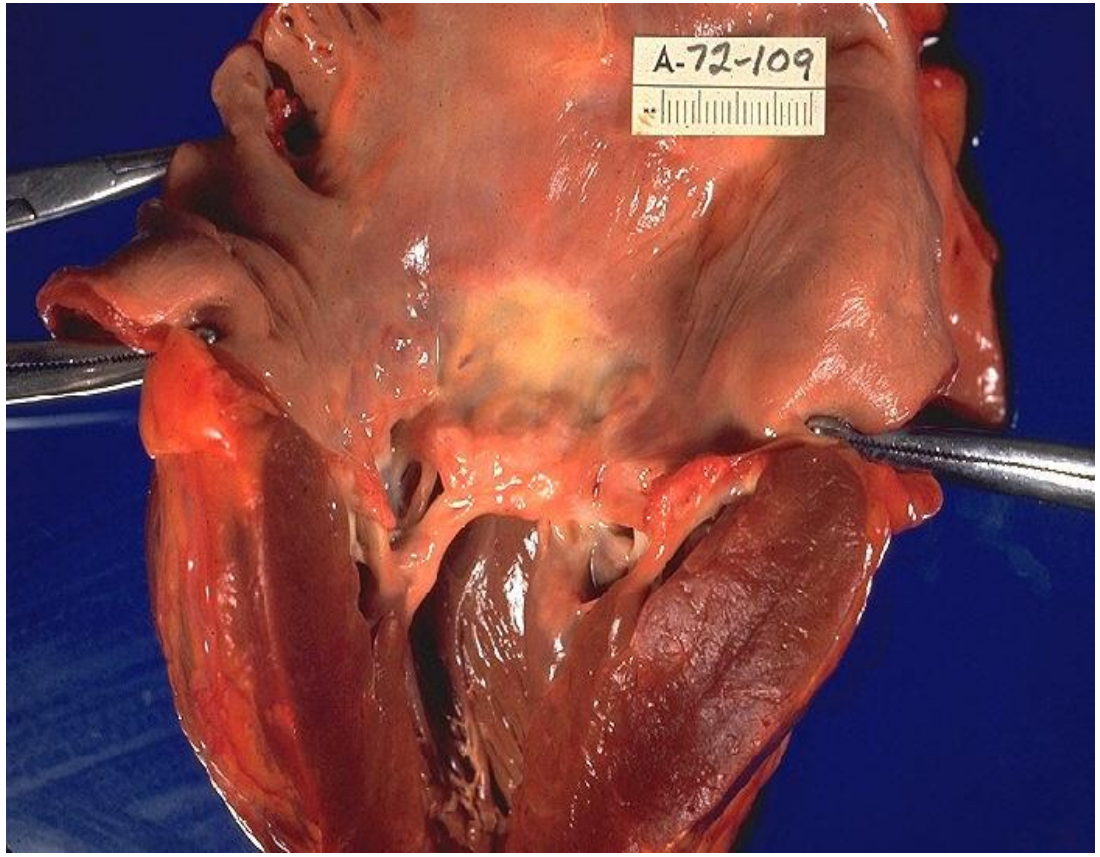
- During a Strep. infection activated antigen presenting cells such as macrophages present the bacterial antigen to helper T cells
- Helper T cells subsequently activate self reactive B cells and induce the production of antibodies against the cell wall of Streptococcus
- However the antibodies may also react against the myocardium and joints, producing the symptoms of rheumatic fever


Environmental factors, especially overcrowding
Precipitating event: infection with a strain of group A streptococcus carrying specific virulence factors
Repeated or ongoing infections possibly driving the valvular inflammatory response
Repeated group A streptococcus infections
Susceptible host
Priming of immune response
First episode of ARF
RHD
Episodes of recurrent ARF
Molecular mimicry between group A streptococcus antigens and host tissues
Exaggerated T-cell mediated immune response
Genetically determined host factors

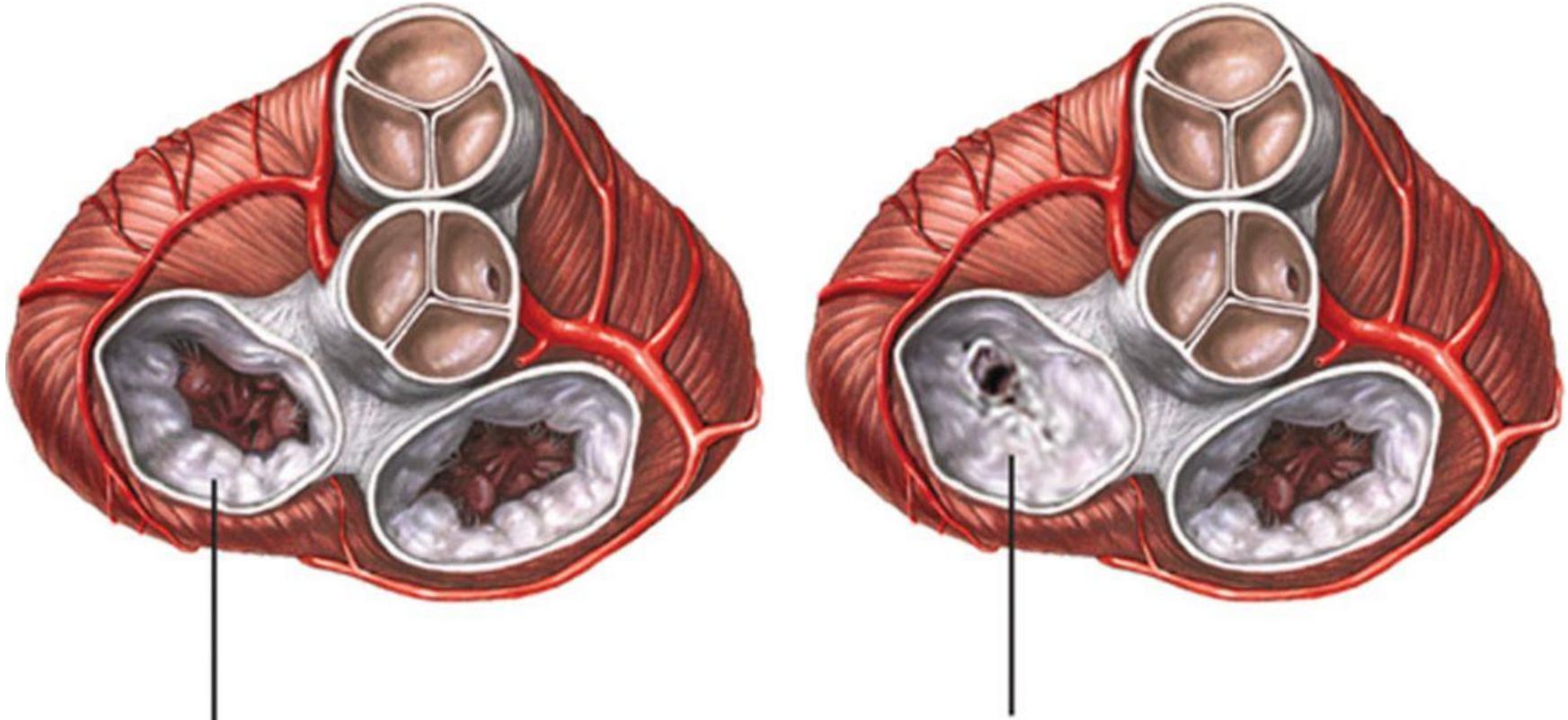
- Up to 60% of patients with ARF progress to Rheumatic Heart Disease

- The endocardium, pericardium, or myocardium may be affected (pancarditis)

- Valvular damage is the hallmark of rheumatic carditis. The mitral valve is almost affected



Left ventricle has been cut open to display characteristic severe thickening of mitral valve, thickened chordae tendineae, and hypertrophied left ventricular



Normal
mitral valve

Rheumatic mitral valve
(with stenosis)

A.D.A.M.

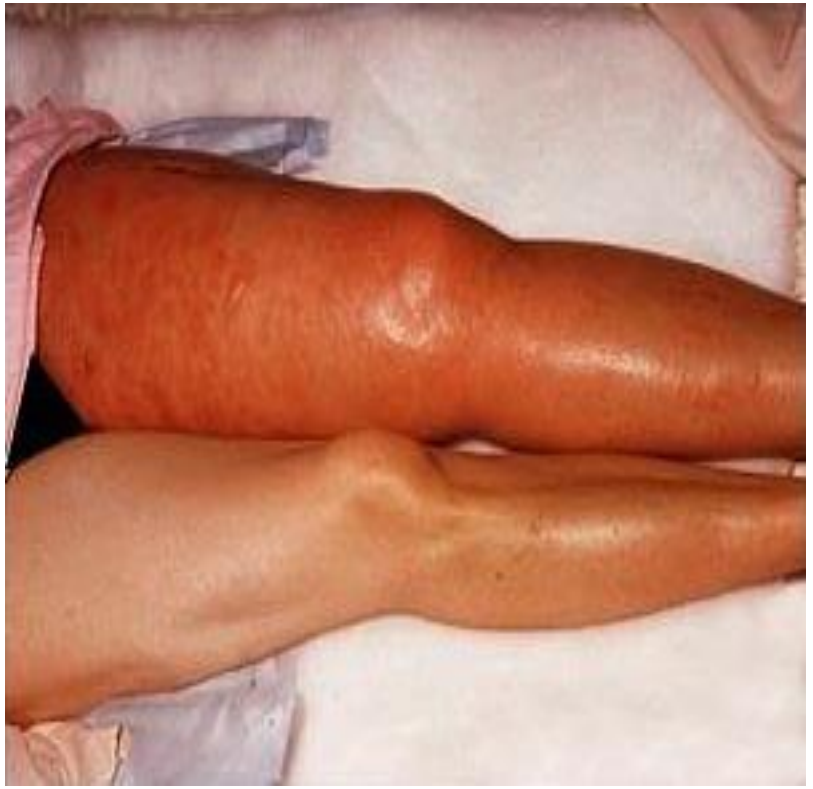
Clinical Presentation

Joints (arthritis)

- This is usually polyarthritis, sometimes flitting from joint to joint (migratory), affecting the larger joints more than the smaller ones.

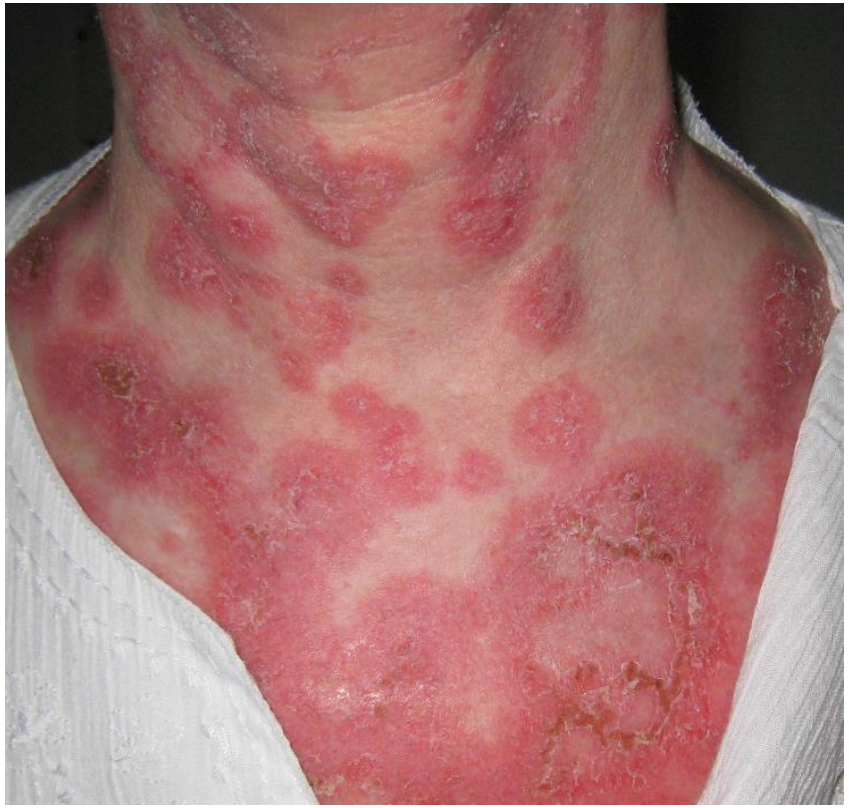
- Swelling, redness and tenderness are the common findings and occasionally joint effusions

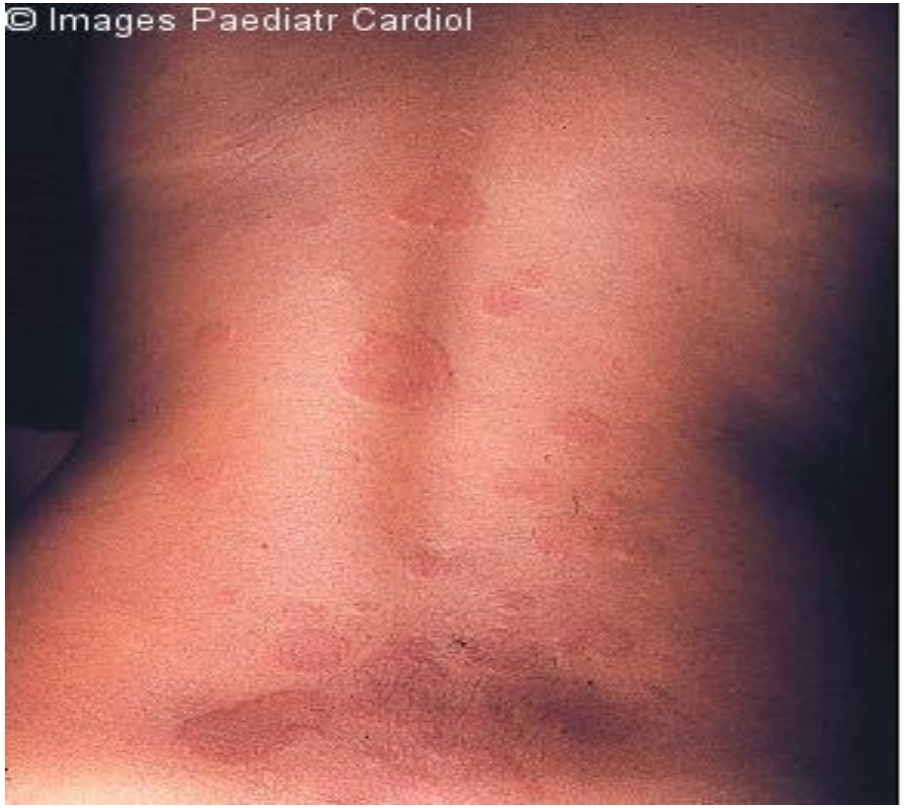
Inflamed Keen Joint



Skin (Erythema Marginatum)

•Skin lesions: The classical erythema marginatum—lesions with prominent margins slightly raised





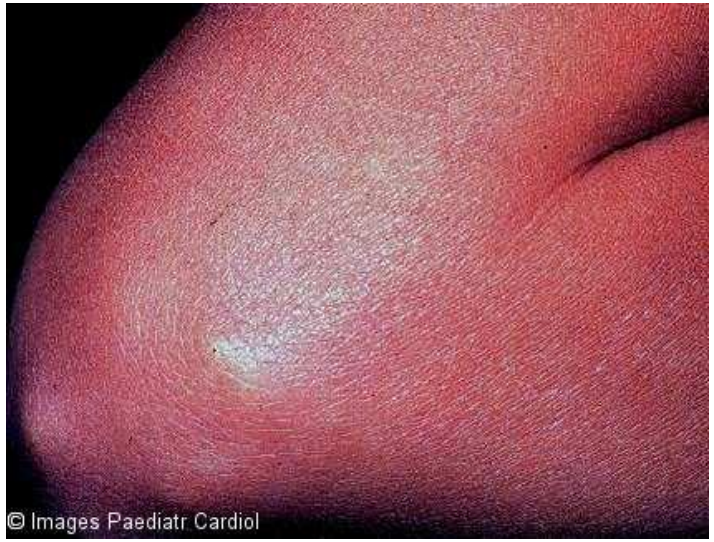
Central nervous system (chorea)

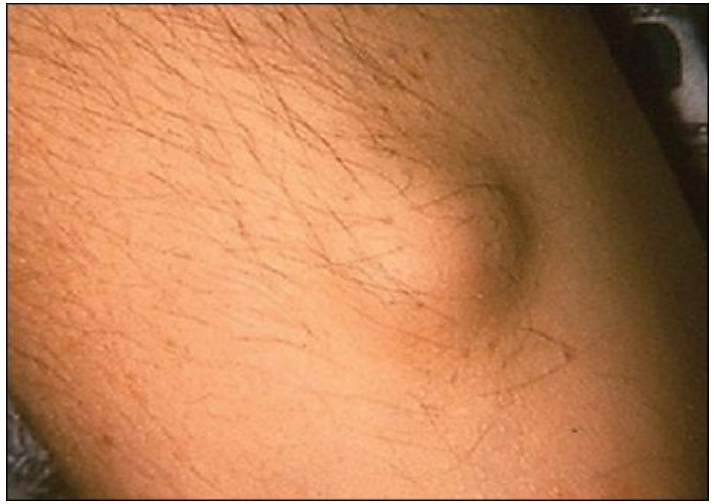
- Sydenham's chorea
- The choreiform movements affect particularly the head and the upper limbs
- They may be generalized or restricted to one side of the body (hemi-chorea)
- Chorea eventually resolves completely, usually within 6 weeks

Subcutaneous nodules

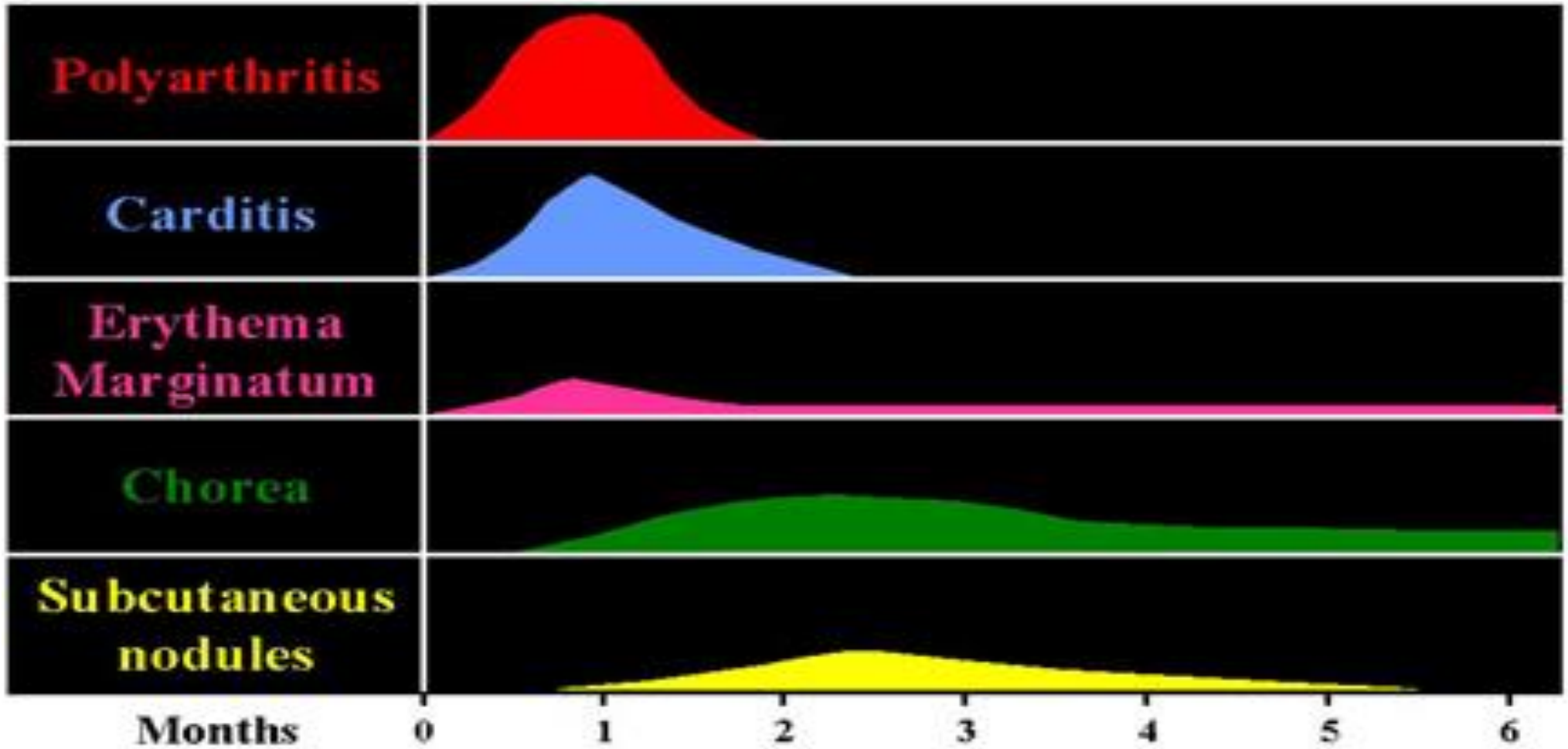
- Subcutaneous nodules : These are painless, round, firm lumps overlaid by normal looking skin

- They range from a few millimeters to 1.5 cm in diameter, and are localized over bony prominences like the elbow, shin and spine. They sometimes last longer than a month





Clinical Manifestations of Acute Rheumatic Fever



Investigation of Rheumatic Fever

- Anti-streptolysin O (ASO) titer
  - At least 80% of patients with ARF have an elevated anti-streptolysin O titer at presentation
    - Rising titer is more convincing
  - Anti-DNAse B
  - Anti-hyaluronidase test
- Throat culture for group A streptococci (obtain 2 or 3 cultures)

Rheumatic Fever – Clinical Course

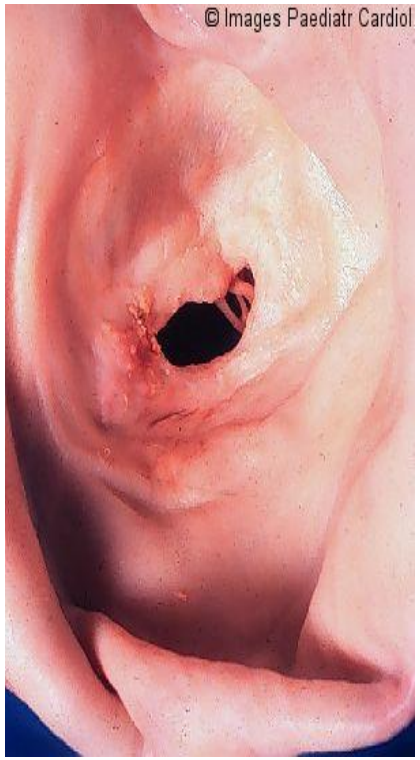
- Subsequent attacks
  - Increased vulnerability to reactivation of disease with subsequent strep infections
  - Same symptoms with each attack
  - Carditis worsens with each attack
  - Heart valves are frequently deformed (mitral)
  - Heart failure develops after decades

Acute, recurring, chronic

- Symptoms prone to recur with subsequent Strep. Infections

- Chronic disease leads to fibrosis (chordae of heart valves + valve cusps)

Stenotic mitral valve seen from left atrium



Opened stenotic mitral valve

Treatment of Rheumatic Fever

- Treat first strep throat infection with **penicillin**
- Treat other manifestations **symptomatically**
- **Prophylactic** long term anti-strep therapy given to anyone who has had rheumatic fever

Take home message

- Rheumatic heart disease results from **cross reacting antibodies** binding the heart valves
- Repeated attacks of Streptococcal throat infection over the years damage heart valves resulting in either **stenotic or incompetent** heart valves

- Treatment involves **surgical** replacement of the damaged heart valves

- In patients with rheumatic fever long term administration of **penicillin** is recommended for prevention of future infections by group A Streptococcus

Thank you