Rheumatic Heart Disease

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Objectives

- To understand 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

- Individual (HLA) susceptibility is also important
- Antigen-presenting cells bearing the HLA-DR7 molecule from RHD patients preferentially recognize heart-tissue protein

  (Guilherme L, Kalil J. Ann N Y Acd Sci 2007,1107:426-433)
- Other views in the literature exist, due to

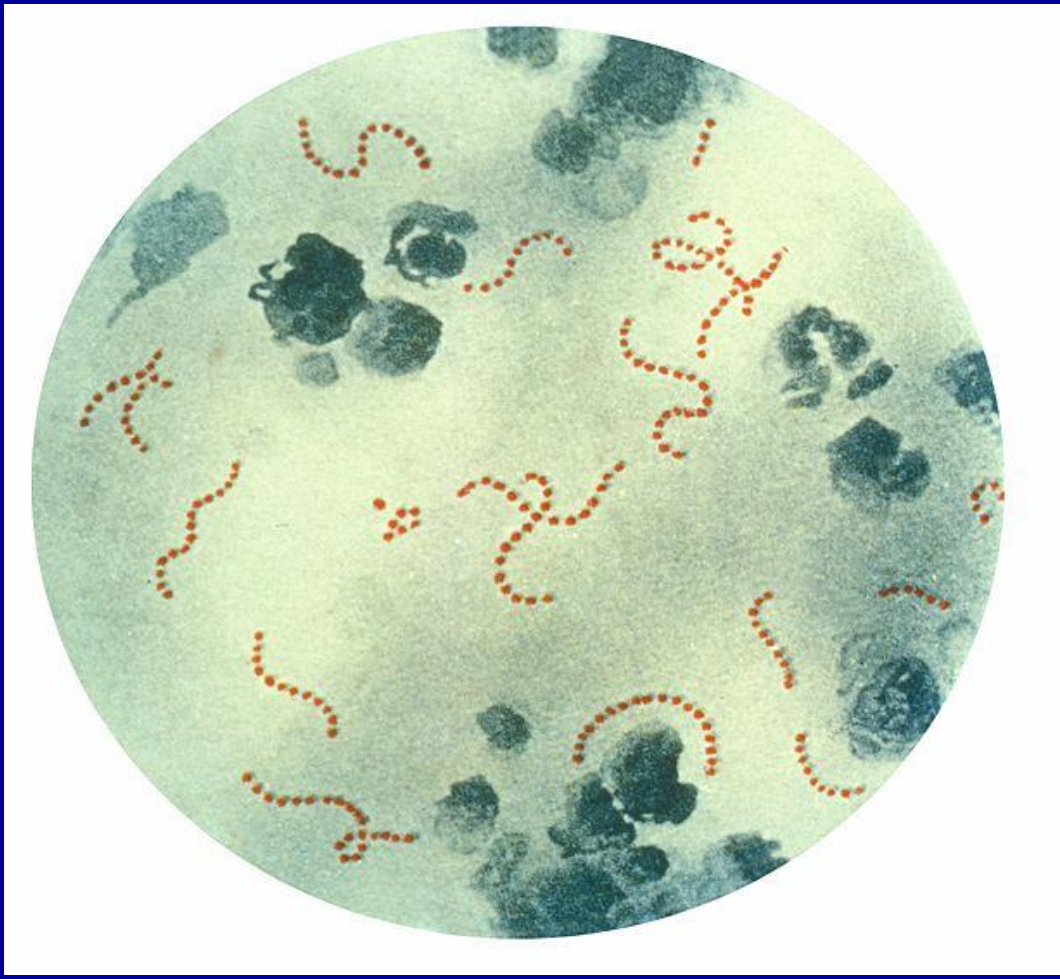
  + The various HLA-typing methods.
  + Ways of grouping the cases.

Rheumatic fever

- Rheumatic fever is an inflammatory disease which may develop after a Group A Streptococcal infection such as:
  - Strep. throat infection or scarlet fever
- Can involve the heart, joints, skin, and brain
- It commonly appears in children ages 5 through 15

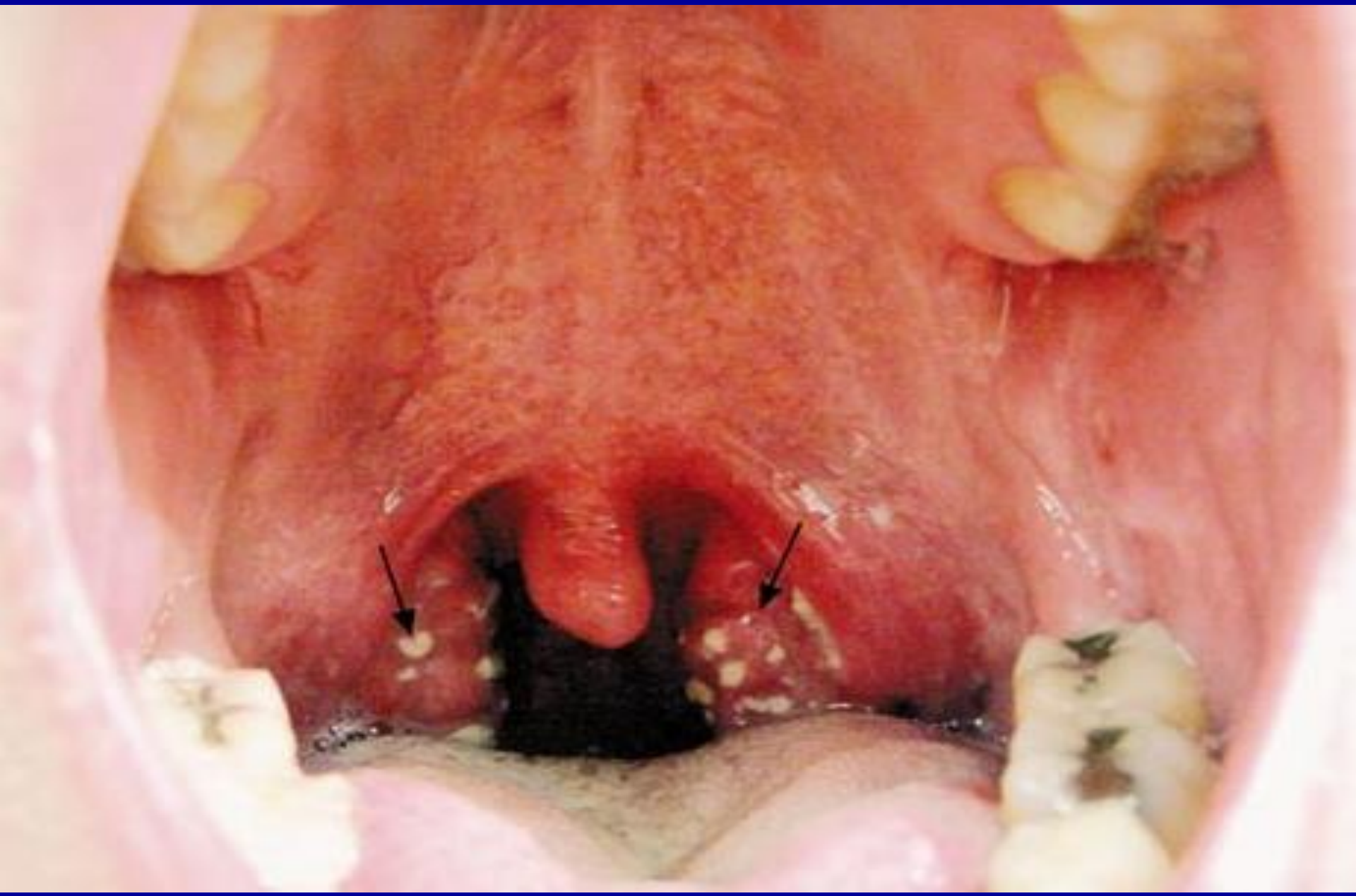
Organism

- 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



Nimishikavi S, Stead L Streptococcal Pharyngitis – Images in Clinical Medicine. NEJM 2005: 352:e10.

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

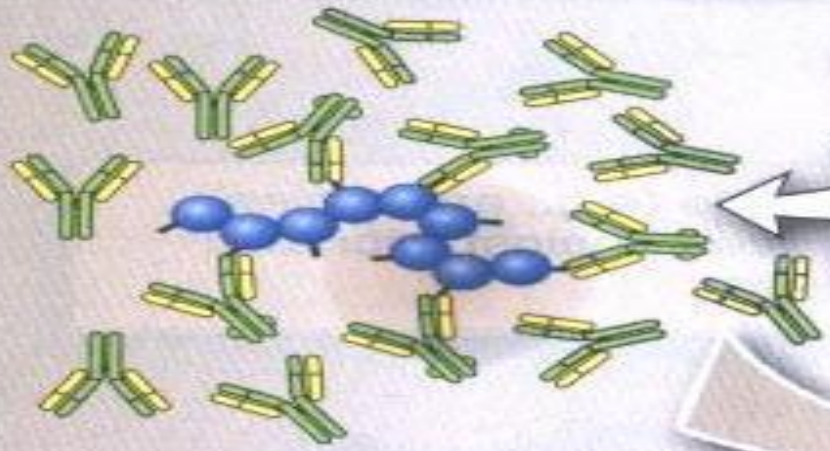
- Rheumatic fever affect the peri-arteriolar connective tissue
- It is believed to be caused by antibody cross-reactivity
- This cross-reactivity is a Type II hypersensitivity reaction and is termed *molecular mimicry*

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

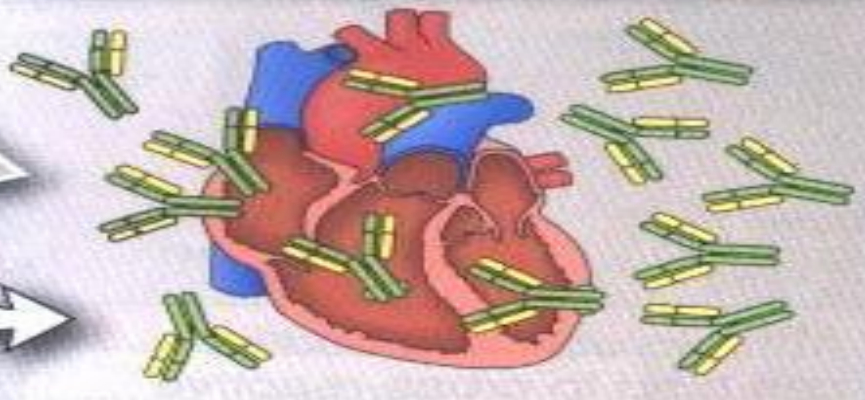
- The antibodies which the immune system generates against the "*M proteins*" may cross react with cardiac myofiber protein myosin and smooth muscle cells of arteries, inducing cytokine release and tissue destruction

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

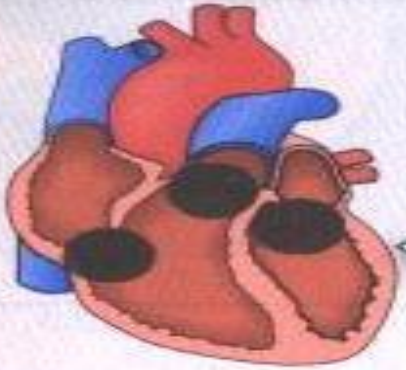
Group A Strep present in throat infection; expresses large amounts of M protein



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

Rheumatic Valve Model

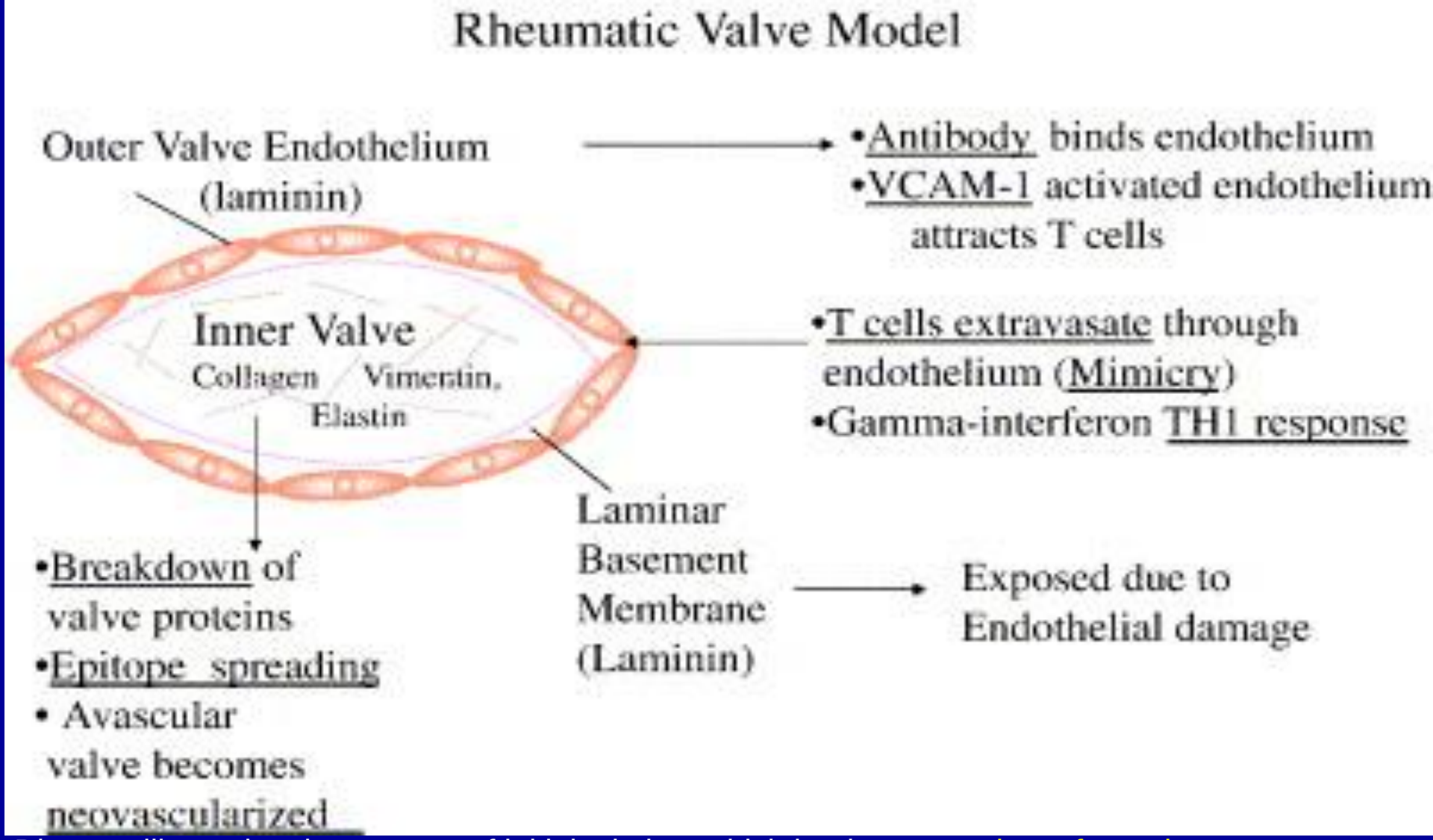
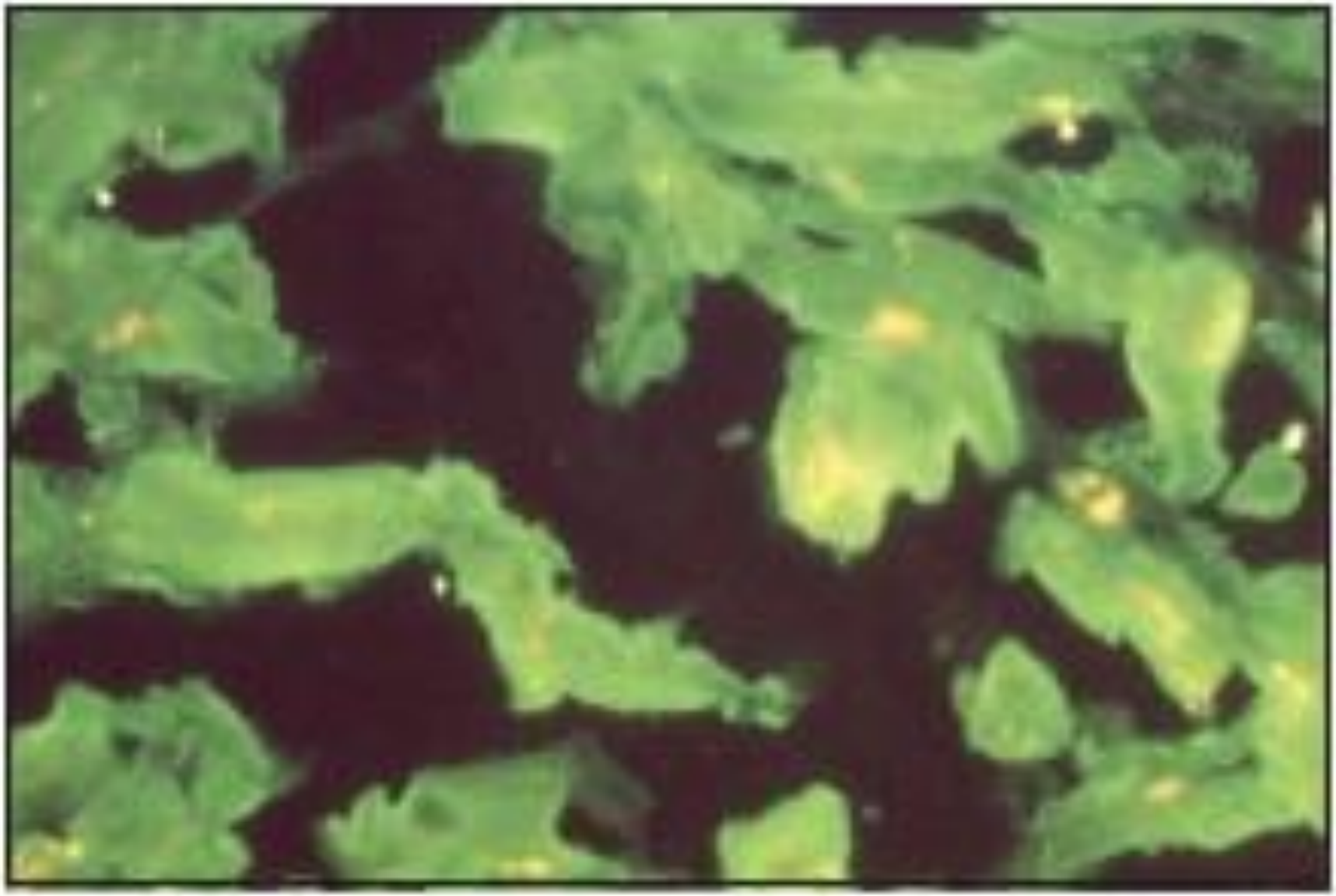


Diagram illustrating the process of initial mimicry which leads to granuloma formation, gamma interferon production and scarring in the valve. After the initial process has developed inflammation in the valve, other proteins in the valve may then be recognized by the immune system leading potentially to epitope spreading and responses against other valve proteins such as vimentin and collagen.

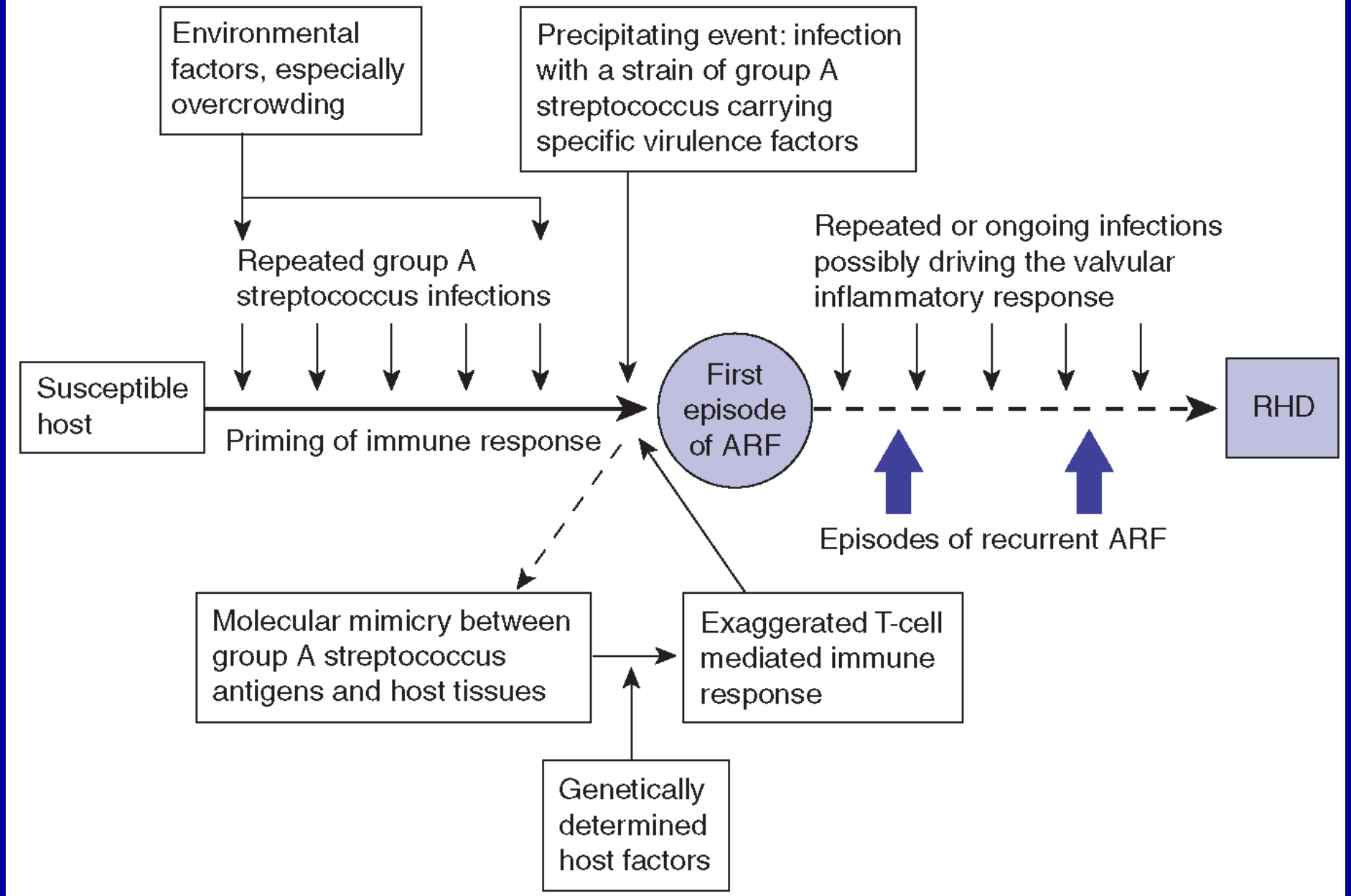
"Molecular mimicry in the autoimmune pathogenesis of rheumatic heart disease" by L. Guilherme; J. Kalil; M.W. Cunningham.



Immunofluorescent staining of heart muscle with serum obtained from an acute rheumatic fever patients

Pathophysiology

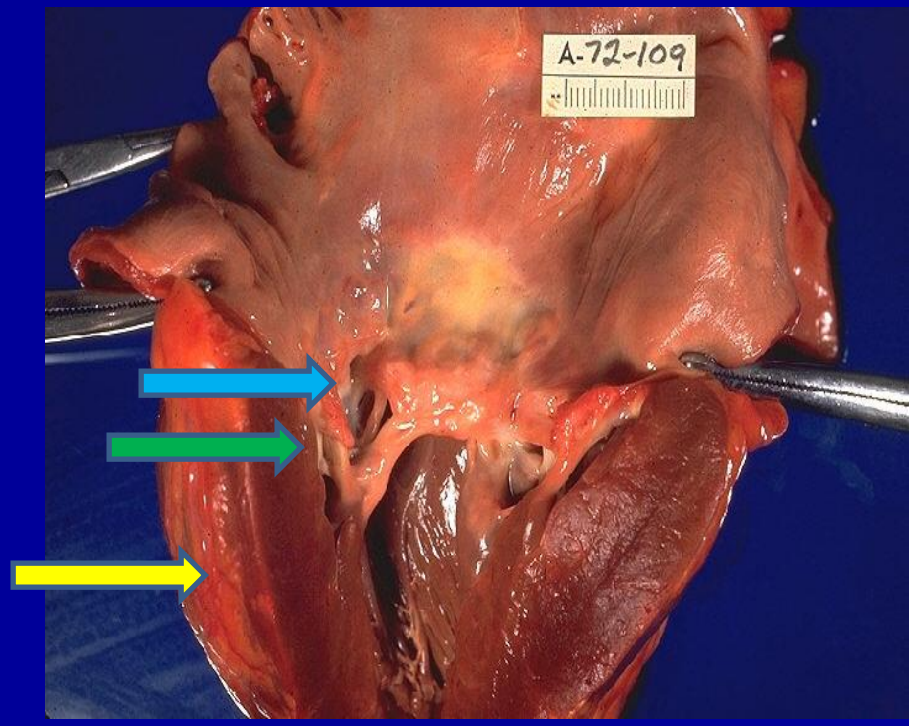
- During a Strep. infection activated antigen presenting cells such as macrophages present the bacterial antigen to helper T cells
- Helper T cells subsequently activate self reactive B cells and induce the production of antibodies against the cell wall of Streptococcus
- However the antibodies may also 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 group A streptococcus infections
Repeated or ongoing infections possibly driving the valvular inflammatory response
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

Clinical Presentation

Heart

- Up to 60% of patients with ARF progress to Rheumatic Heart Disease (RHD)
- only manifestation of ARF with significant potential to cause long-term disability and/or death
- The endocardium, pericardium, or myocardium may be affected (pancarditis)
- Valvular damage is the hallmark of rheumatic carditis. The mitral valve is almost affected



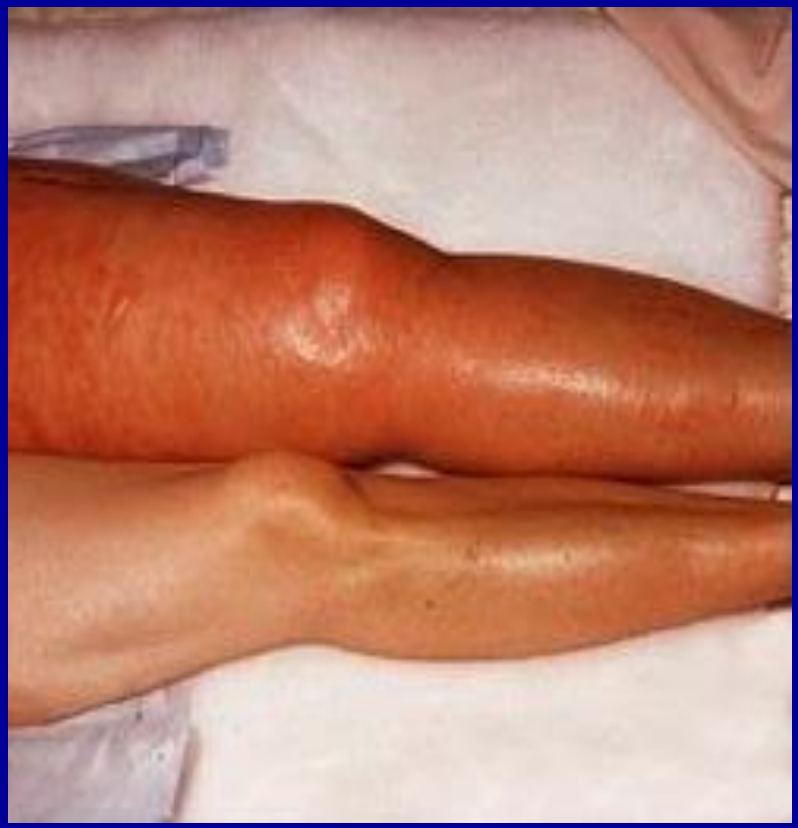
Left ventricle has been cut open to display characteristic severe thickening of mitral valve, thickened chordae tendineae, and hypertrophied left ventricular

Joints (arthritis)

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

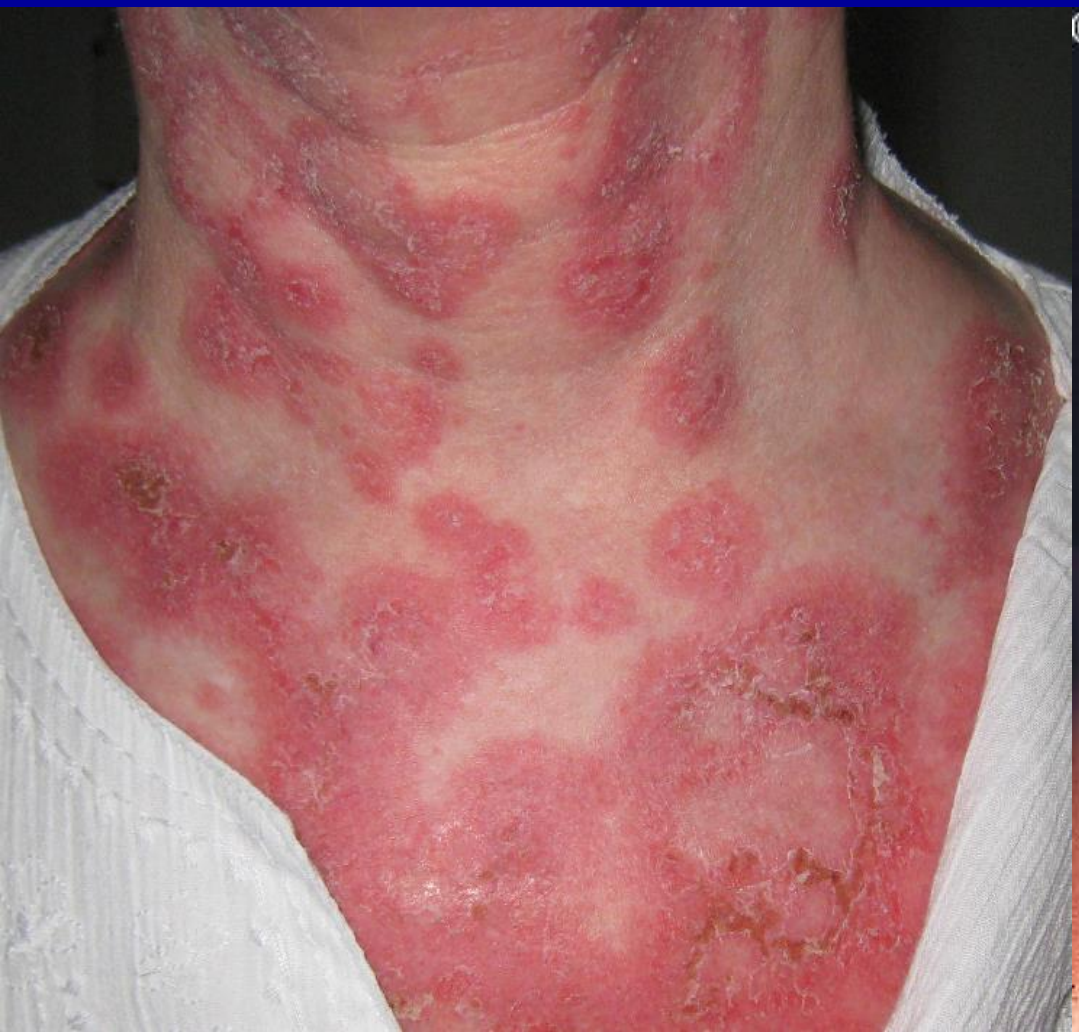
- Swelling, redness and tenderness are the common findings and occasionally joint effusions

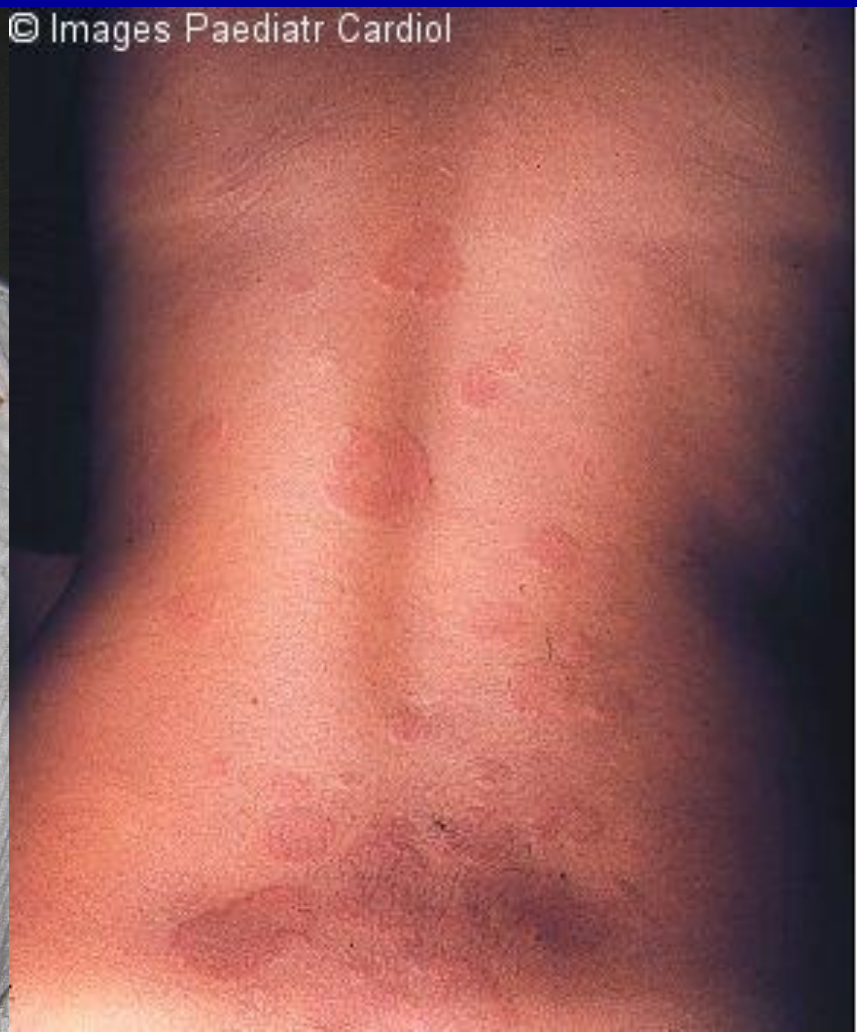
- Inflamed knee Joint



Skin (Erythema Marginatum)

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





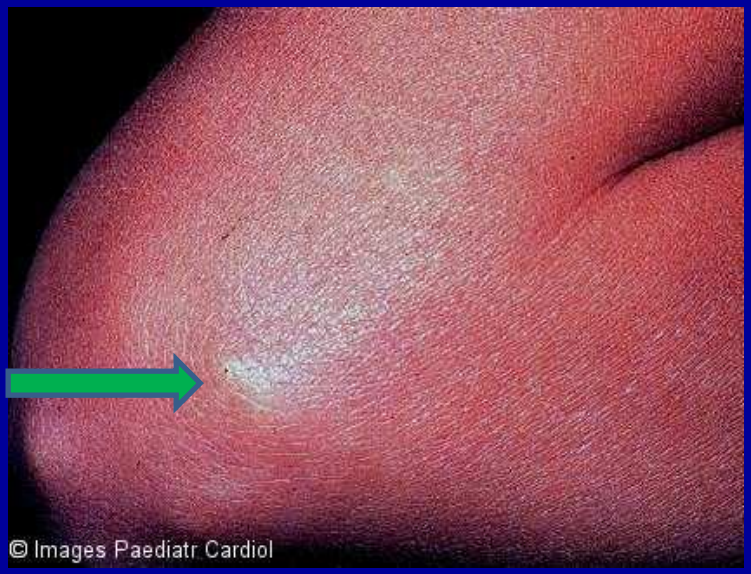
Central nervous system (chorea)

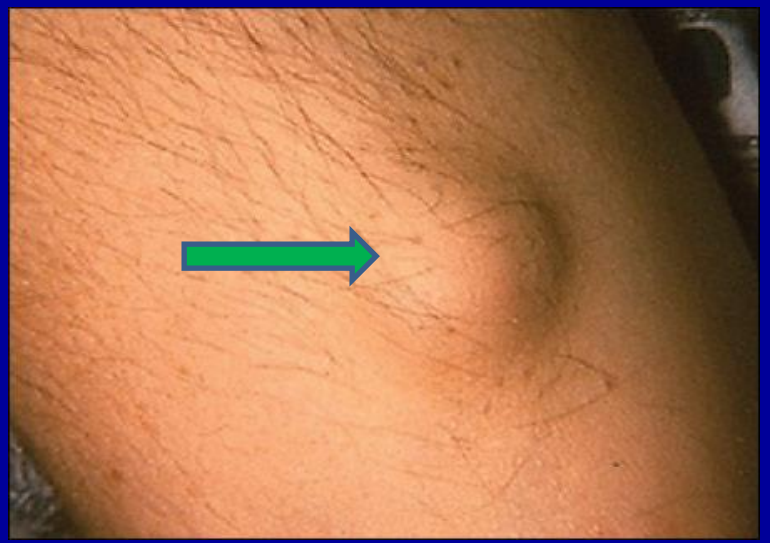
- Sydenham's chorea
- Occurs in children, rare in adults
- The choreiform movements affect particularly the head and the upper limbs
- They may be generalized or restricted to one side of the body (hemi-chorea)
- Chorea eventually resolves completely, usually within 6 weeks
- likely due to molecular mimicry, with autoantibodies reacting with brain ganglioside

Subcutaneous nodules

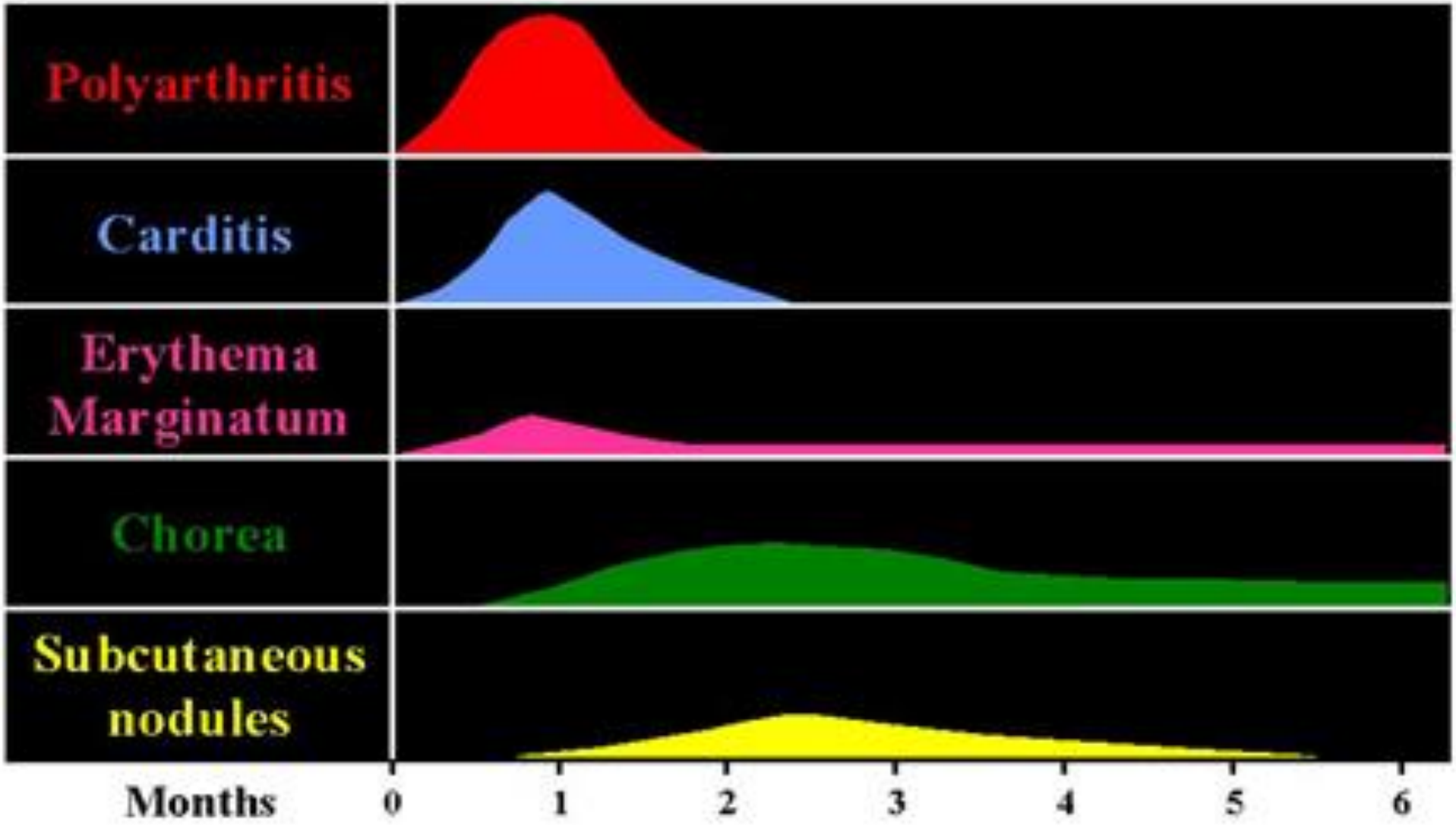
- Subcutaneous nodules : These are painless, round, firm lumps overlaid by normal looking skin

- 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

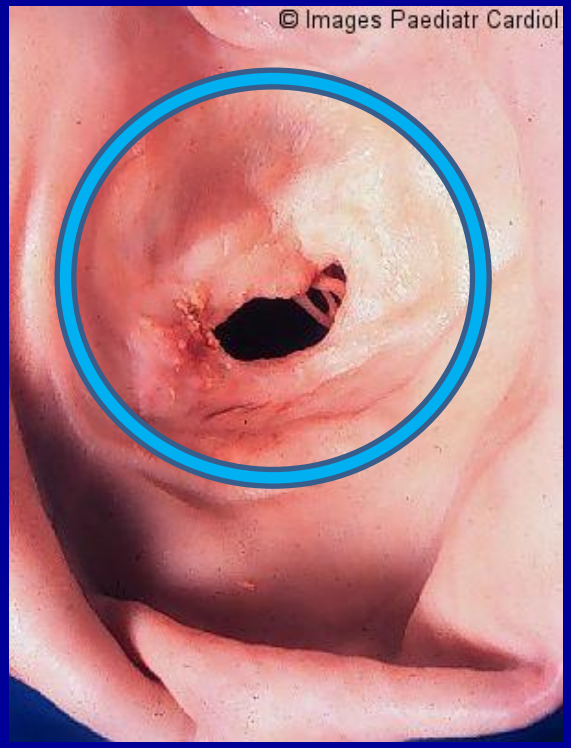
- Anti-streptolysin O (ASO) titer
  - At least 80% of patients with ARF have an elevated anti-streptolysin O titer at presentation
    - Rising titer is more convincing
  - Anti-DNAse B
  - Anti-hyaluronidase test
- Throat culture for group A streptococci (obtain 2 or 3 cultures)

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