

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 Acad Sci 2007,1107:426-433)

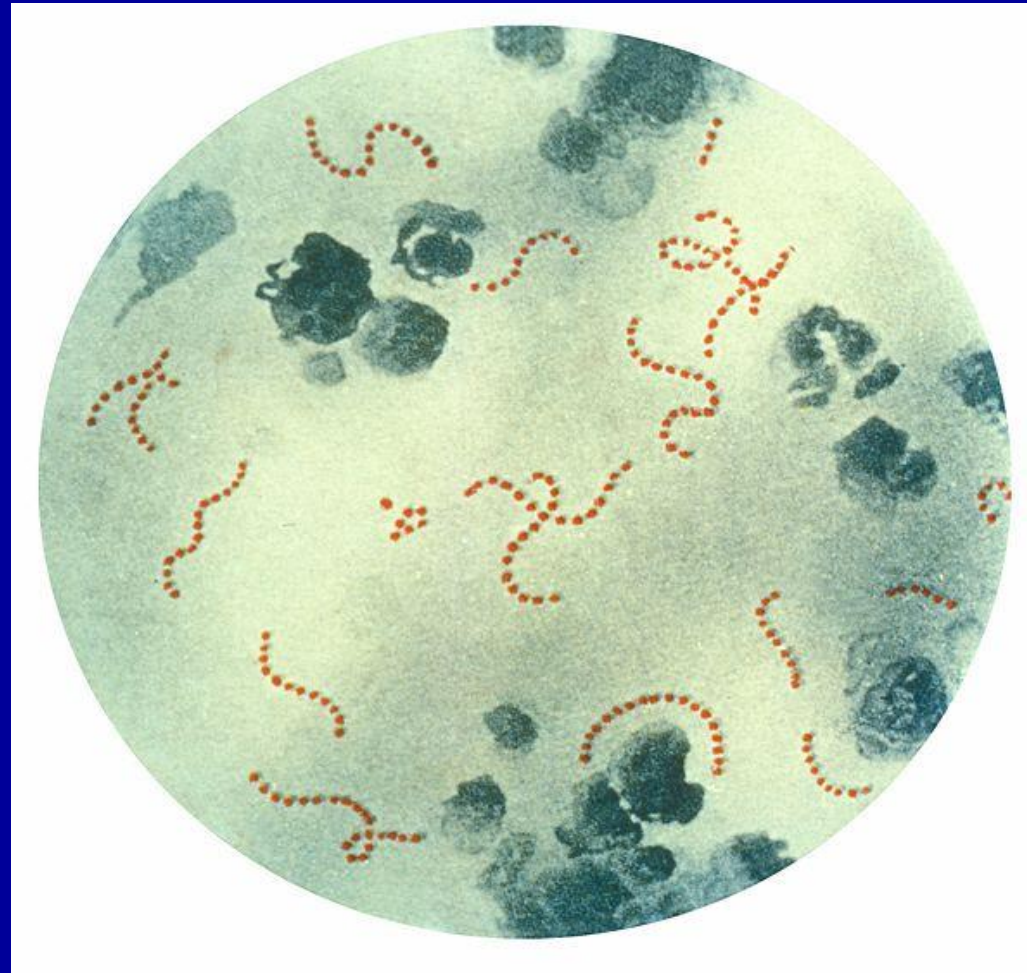
- Other views in the literature exist, due to
 - + The various HLA-typing methods.
 - + Ways of grouping the cases.

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:

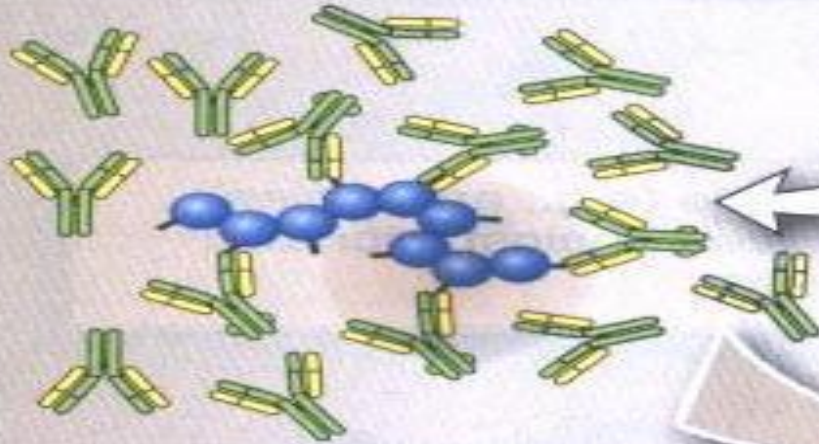
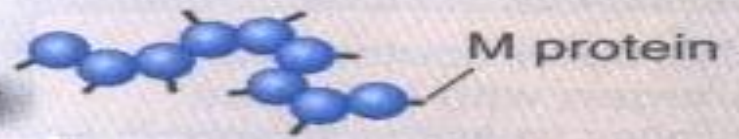
Lyse erythrocytes, leukocytes & platelets

PATHOGENESIS

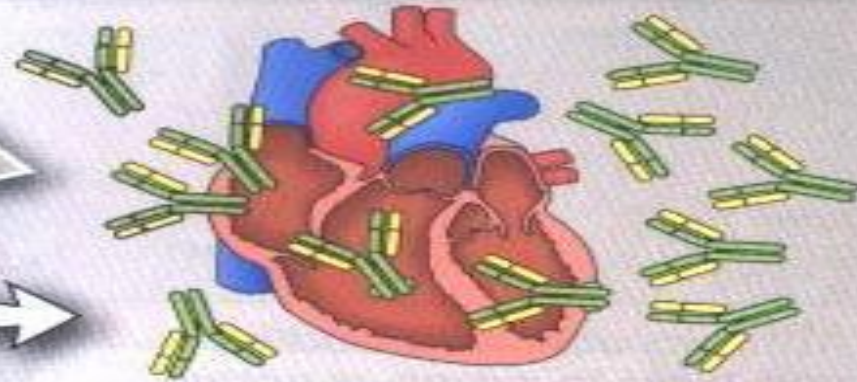
- Rheumatic fever affect the peri-arteriolar connective tissue
- It is believed to be caused by **antibody cross-reactivity**
- This cross-reactivity is a **Type II hypersensitivity** reaction and is termed *molecular mimicry*

- 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**

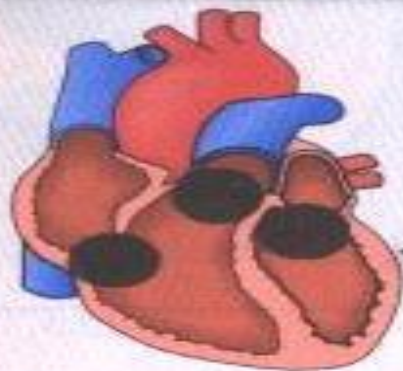
Group A Strep present in throat infection; expresses large amounts of M protein



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

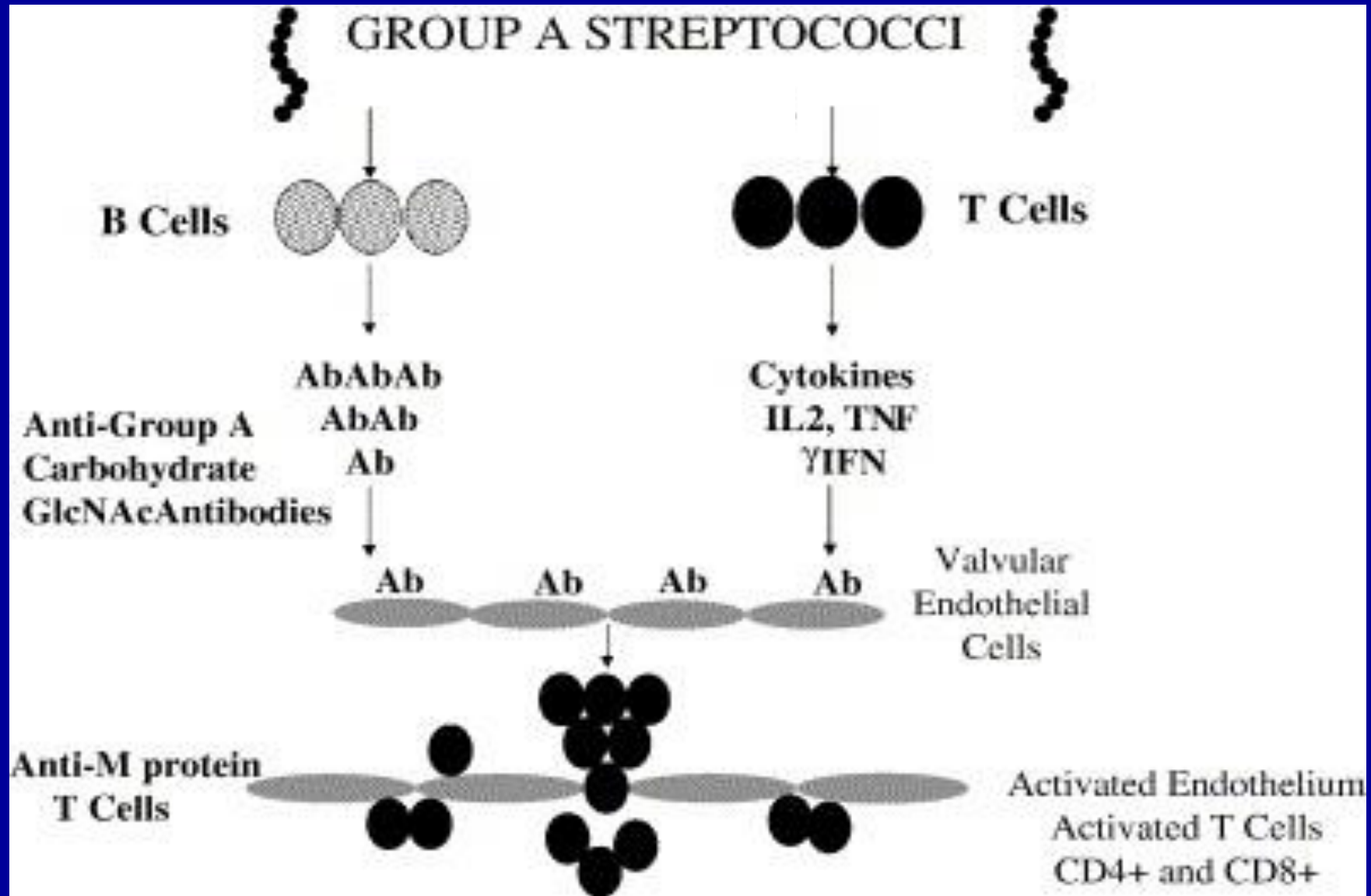


Diagram illustrating the two hit theory of rheumatic heart disease. Group A streptococcal infection leads to the production of anti-group A carbohydrate antibody which cross-reacts with the valve endothelium as well as with the myocardium and **up-regulates vascular cell adhesion molecule-1 (VCAM-1)** on the valve endothelium. T cells adhere to the VCAM-1 on valve endothelium and extravasate into the valve.

Rheumatic Valve Model

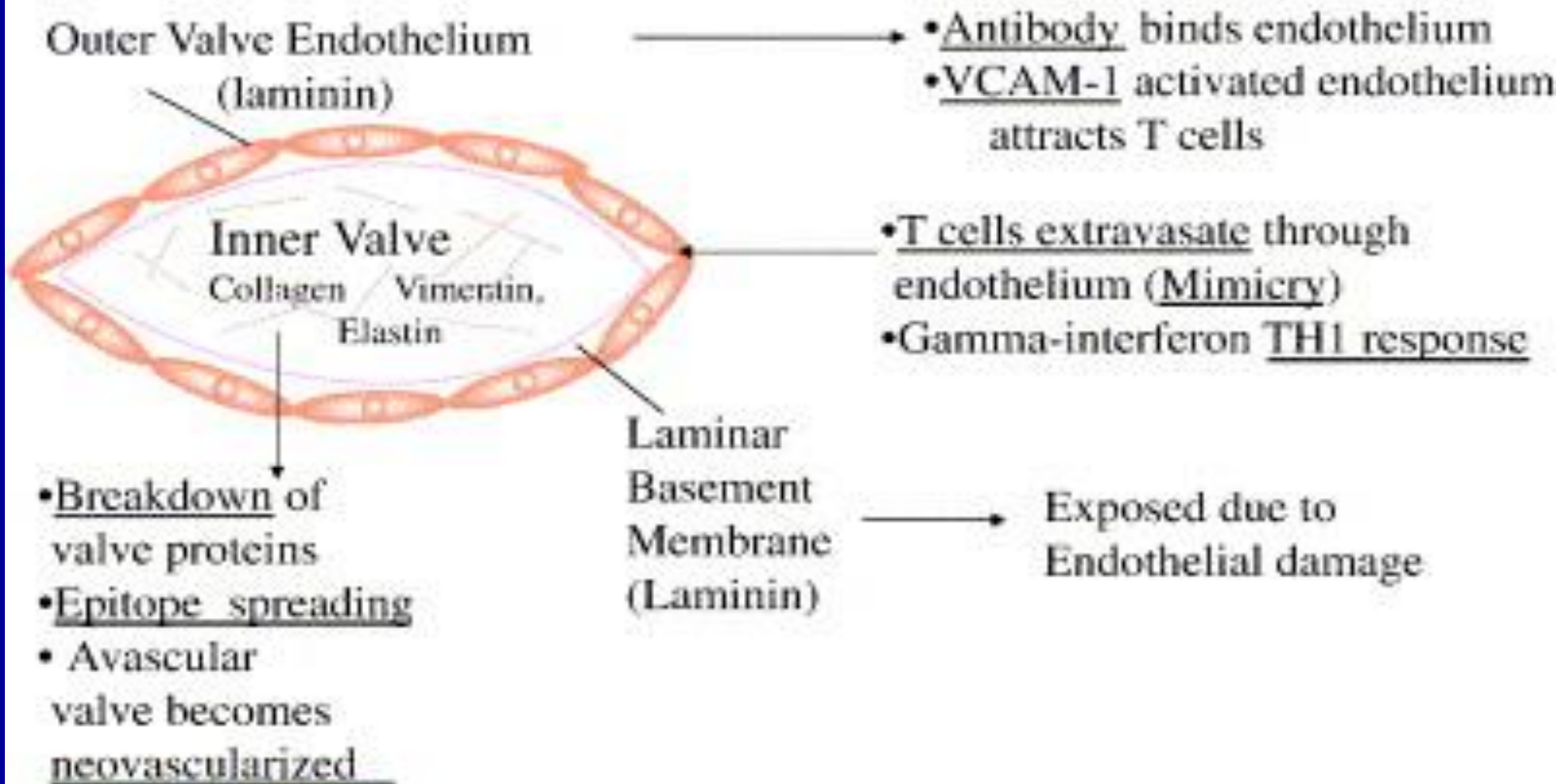
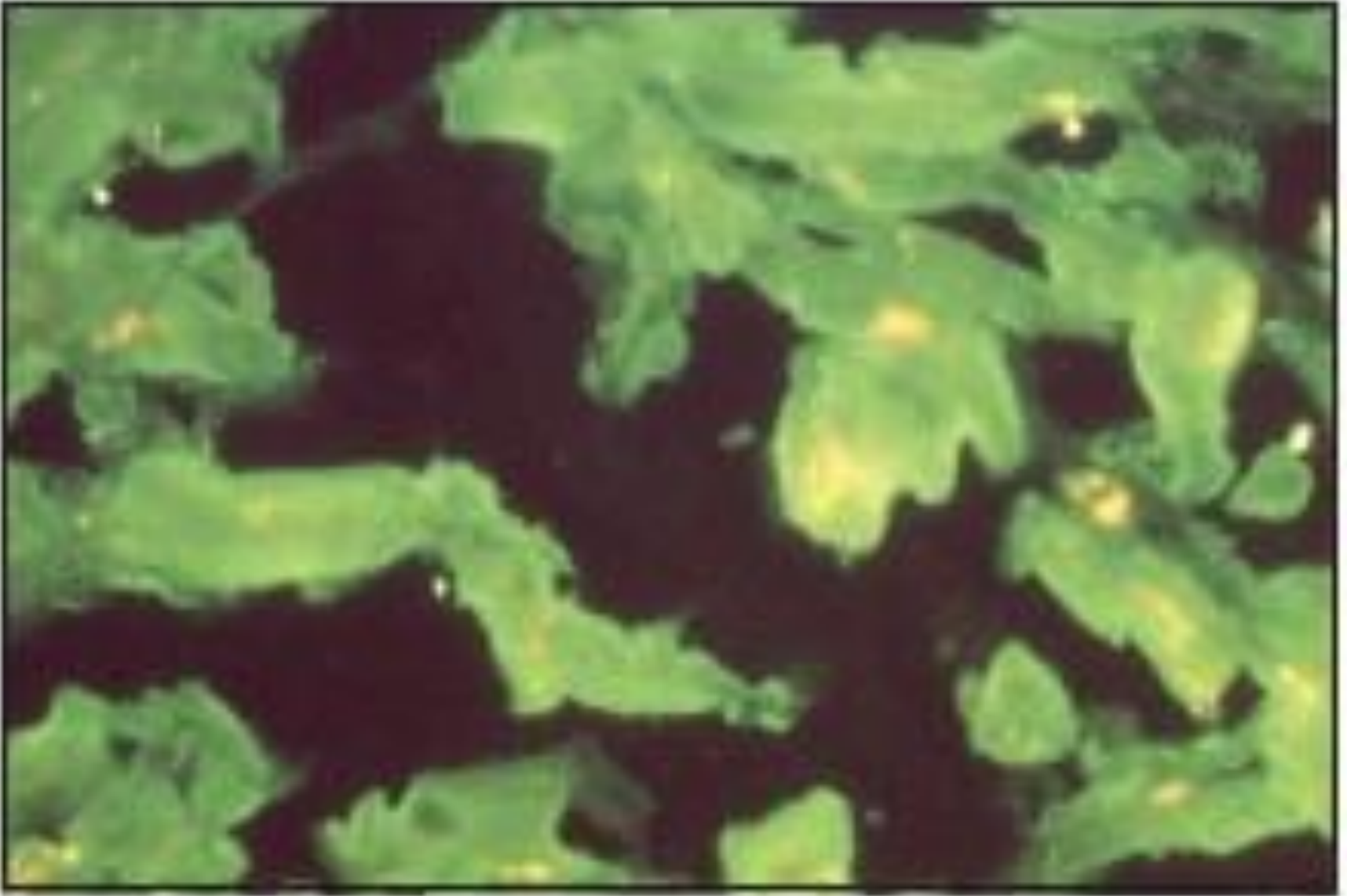


Diagram illustrating the process of initial mimicry which leads to **granuloma formation, gamma interferon production and scarring in the valve**. After the initial process has developed inflammation in the valve, other proteins in the valve may then be recognized by the immune system leading potentially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

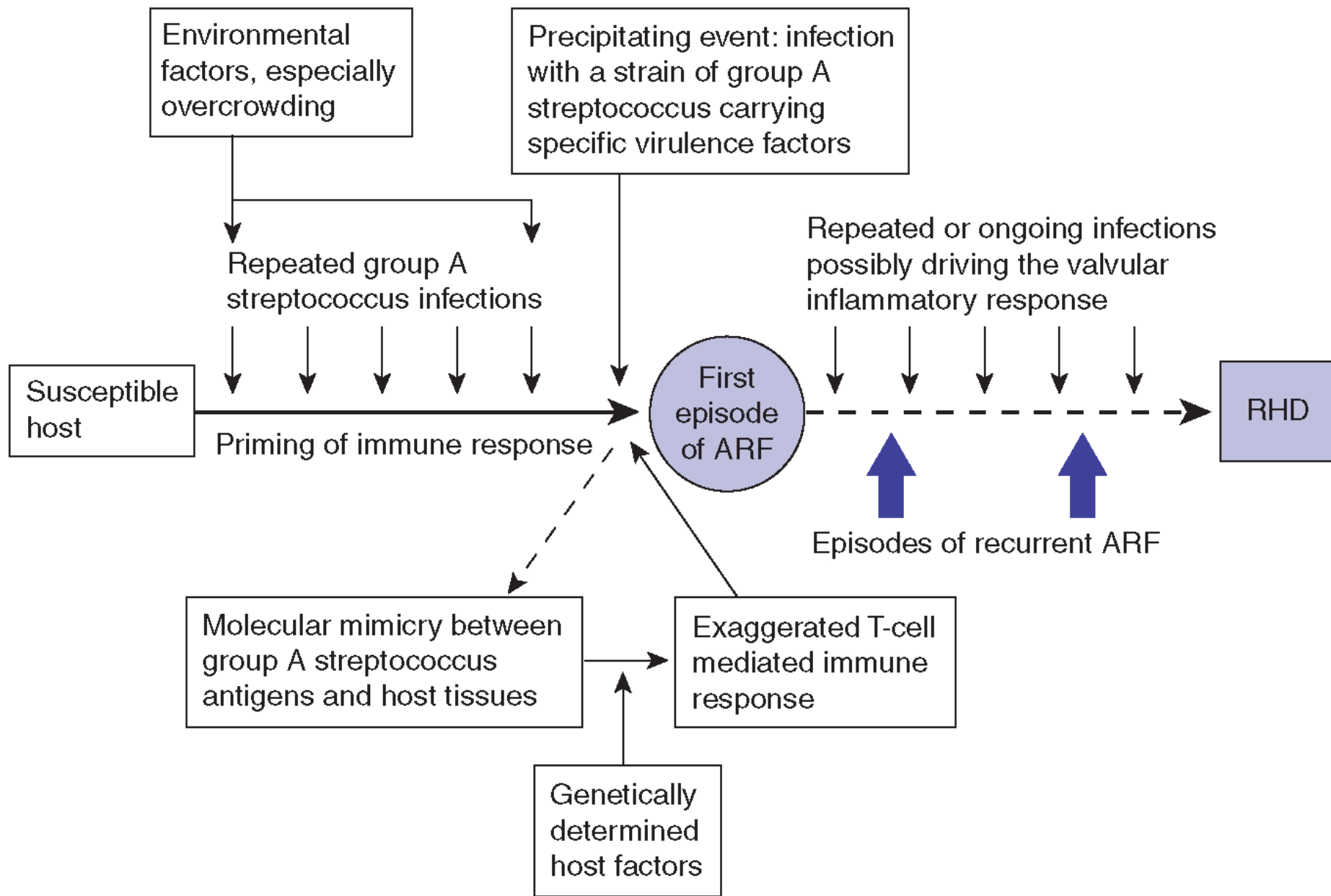
"Molecular mimicry in the autoimmune pathogenesis of rheumatic heart disease" by L. Guilherme; J. Kalil; M.W. Cunningham.



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

Pathophysiology

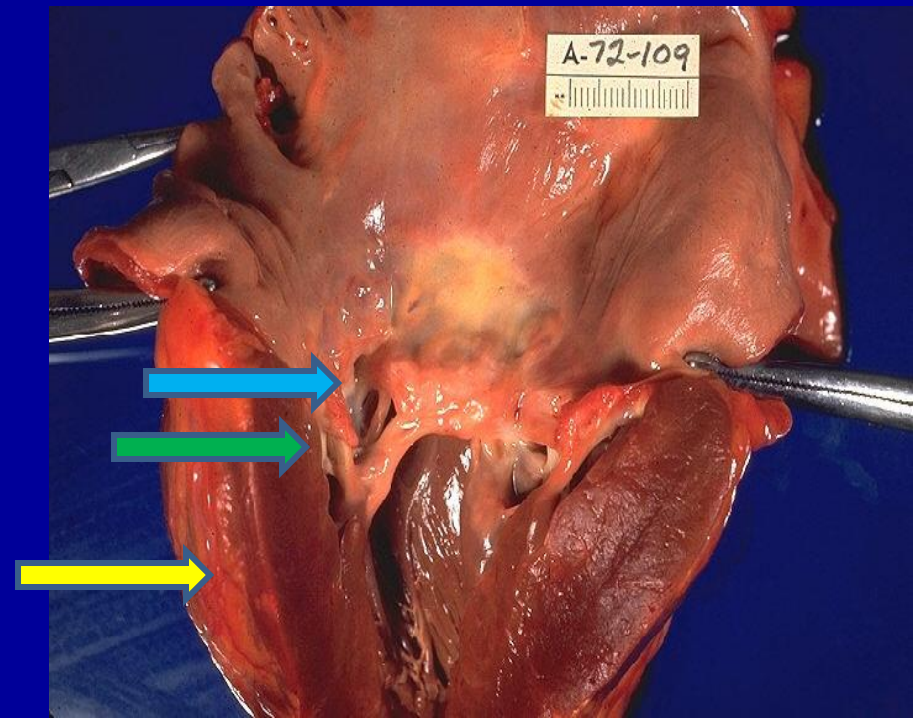
- During a Strep. infection activated antigen presenting cells such as macrophages present the bacterial antigen to helper T cells
- Helper T cells subsequently activate self reactive B cells and induce the production of antibodies against the cell wall of Streptococcus
- However the antibodies may also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



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 **Keen Joint**

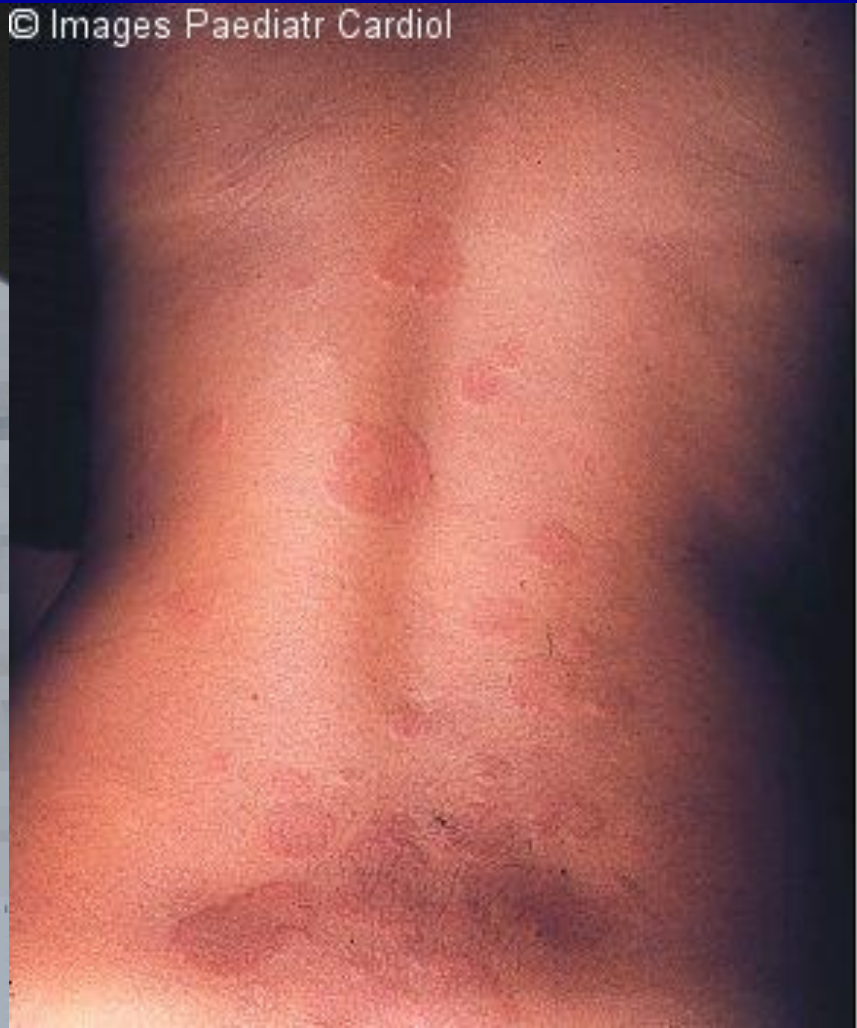


Skin (Erythema Marginatum)

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



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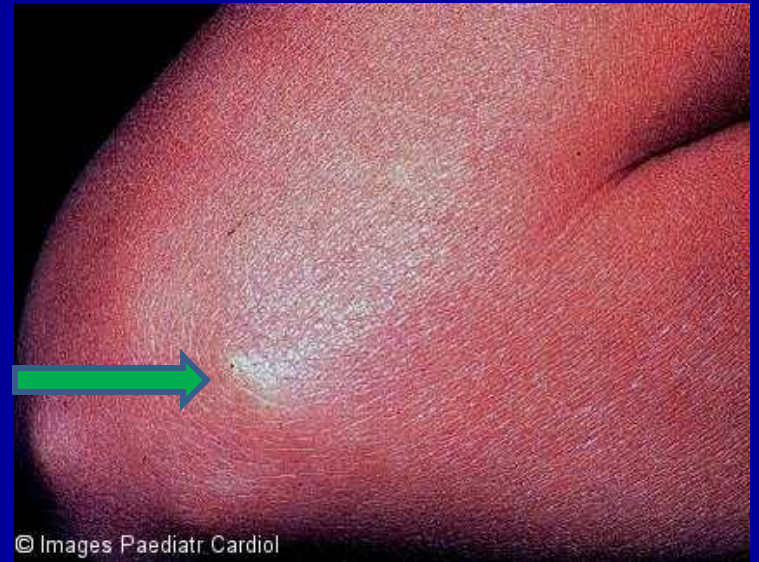
Central nervous system (chorea)

- 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

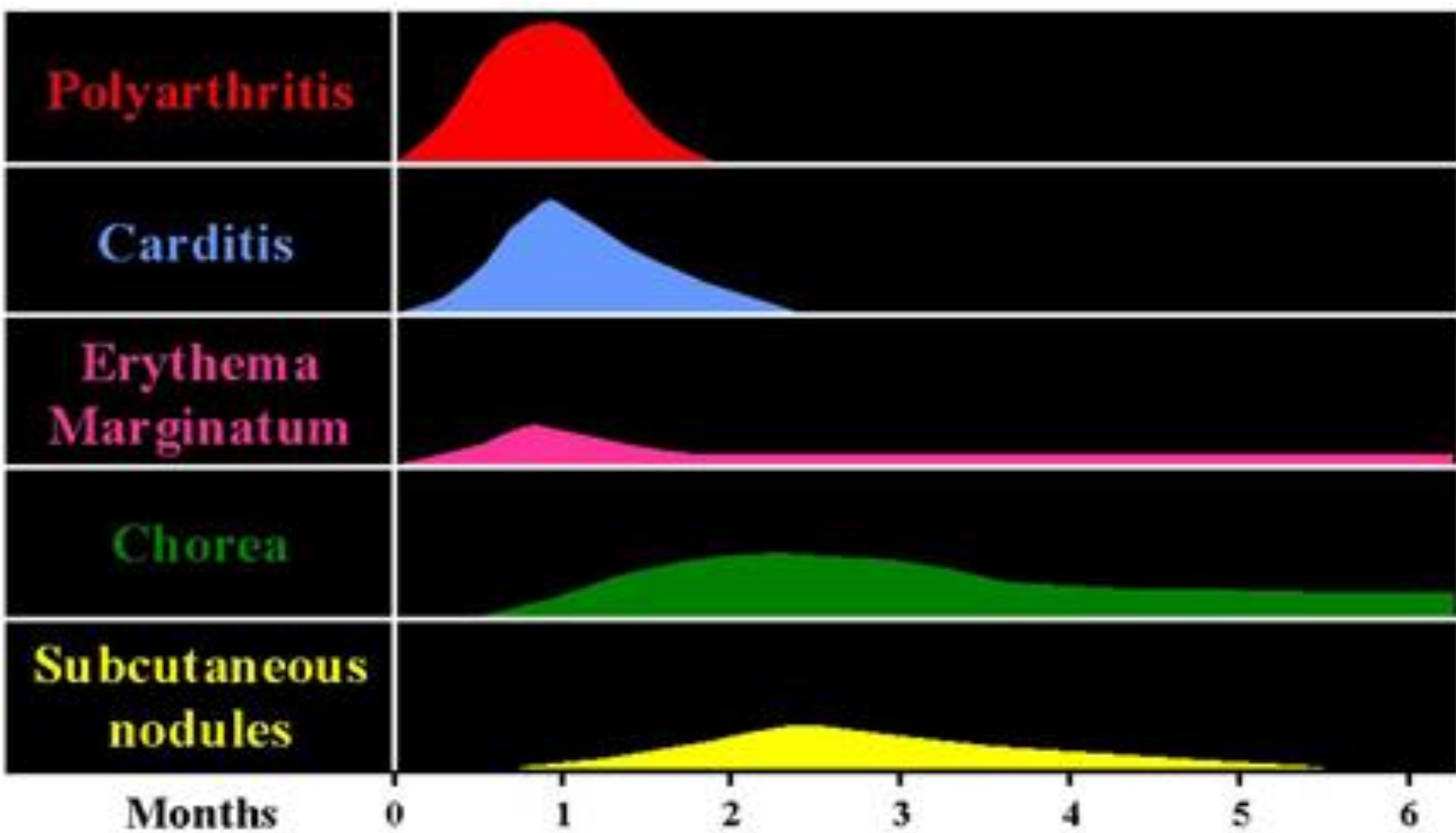


Subcutaneous nodules

- **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