MEDICINE
KING SAUD UNIVERSITY

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CVS Block

Lecture One

Rheumatic heart disease

IMMUNOLOGY

436's TEAMWORK

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 antigen
- To describe rheumatic heart disease as one of the several manifestations of rheumatic fever
- To know signs, symptoms, pathogenesis, treatment and prophylaxis of rheumatic heart disease

- **Important.**
- **Extra notes.**
- **Females notes**
- **Males notes.**

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.

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.

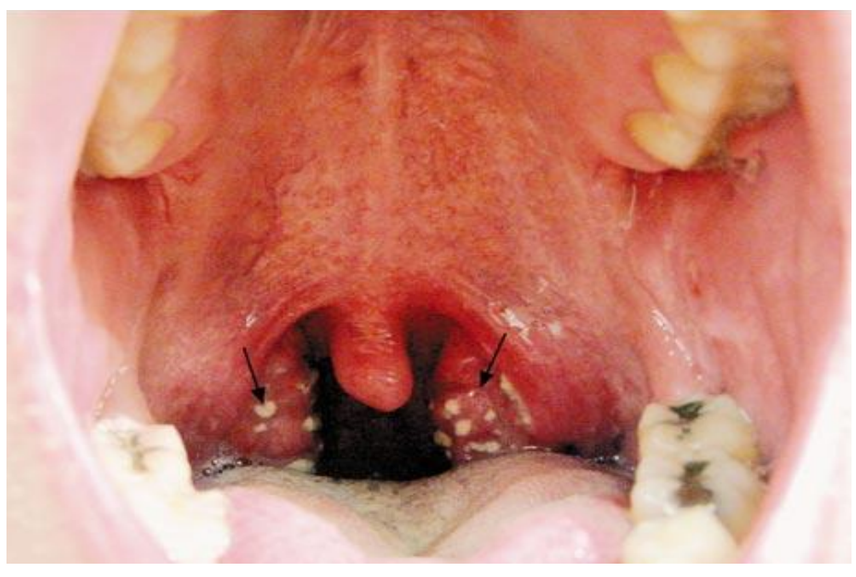
- Individual (HLA) human leukocyte antigen susceptibility is also important.
- Antigen-presenting cells bearing the **HLA-DR7** molecule from RHD patients preferentially recognize heart-tissue protein.
- Other views in the literature (written work) exist, due to:

+ The various HLA-typing methods.

+ Ways of grouping the cases.

Organism

- Caused by **Group A beta-haemolytic 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.

- All cases associated with recent infection (e.g. pharyngitis).

- **Antibody and cellular immune response** cross-reacts with human connective tissue.

M proteins:
Adherence of Streptococcus pyogenes to host cells & inhibiting the host immune response (released by streptococci to facilitate bacterial and viral cells to enter the host cell by countering its immune response)

Hyaluronic acid capsule:
Camouflages the bacterium

Streptokinases:
Dissolve blood clots

Peptidases:
Degrades proteins involved in immune response

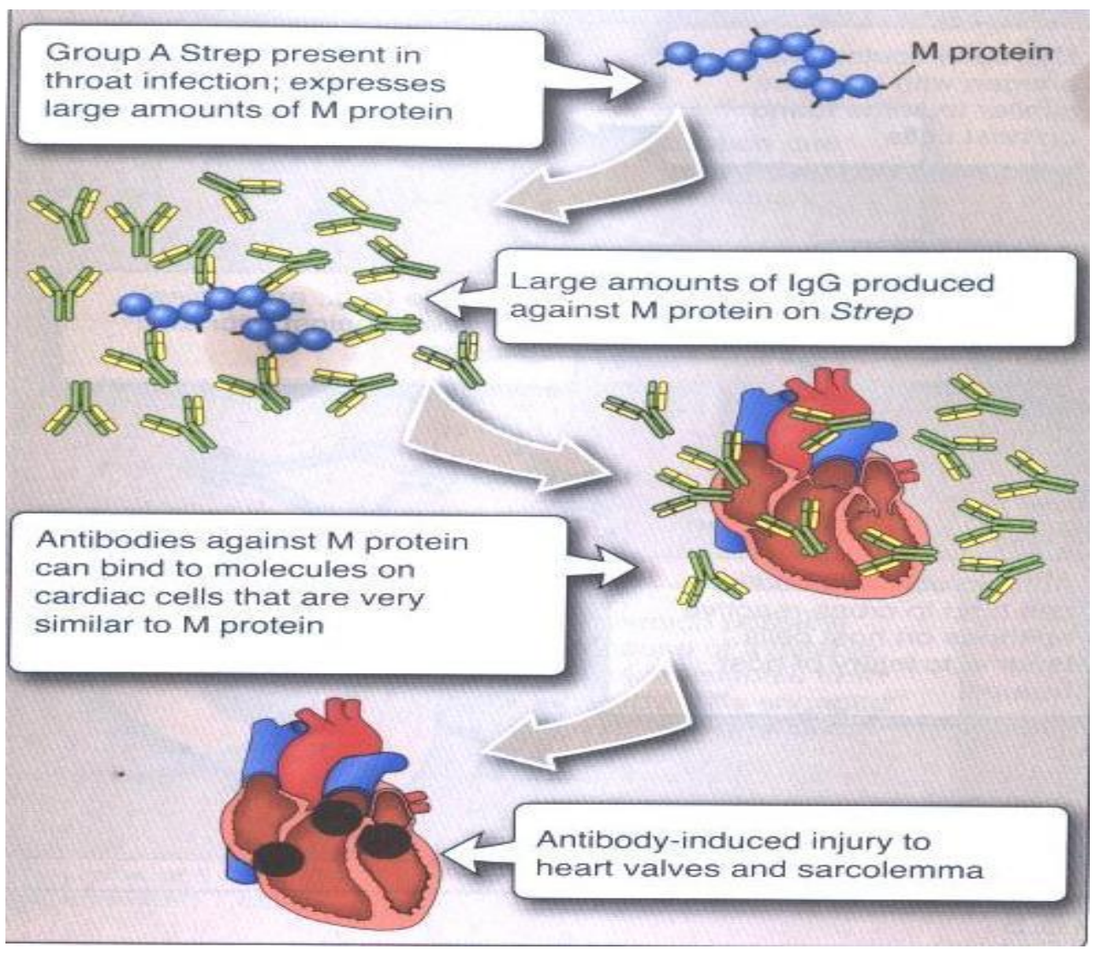
Pyrogenic toxins:
(non specifically activated T cells & stimulate production of inflammatory cytokine which will)
Stimulate fever, rash & shock

Streptolysins:
Lyse erythrocytes, leukocytes & platelets
(part of inhibiting host defense)

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**.

Type I = IgE
Type II = Antibody
Type III = immune complex
Type IV = cell mediated



- 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**.

Recall: the Fc region is the region where antibody attach to its antigen

Pathogenesis

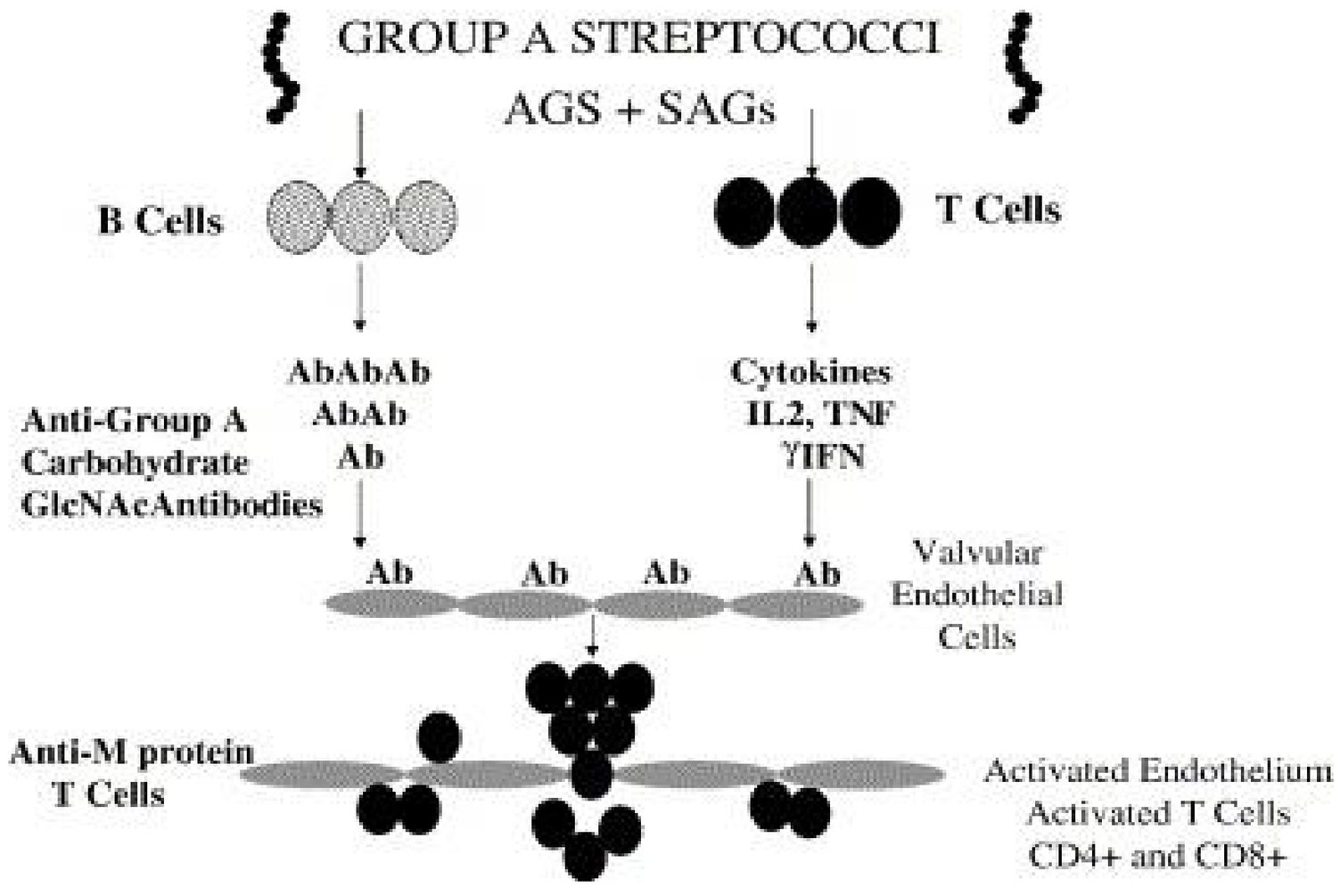


Diagram illustrating the **two hit theory** of rheumatic heart disease. Group A streptococcal infection leads to the production of anti-group A carbohydrate antibody which cross-reacts with the valve endothelium as well as with the myocardium and **up-regulates vascular cell adhesion molecule-1 (VCAM-1)**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

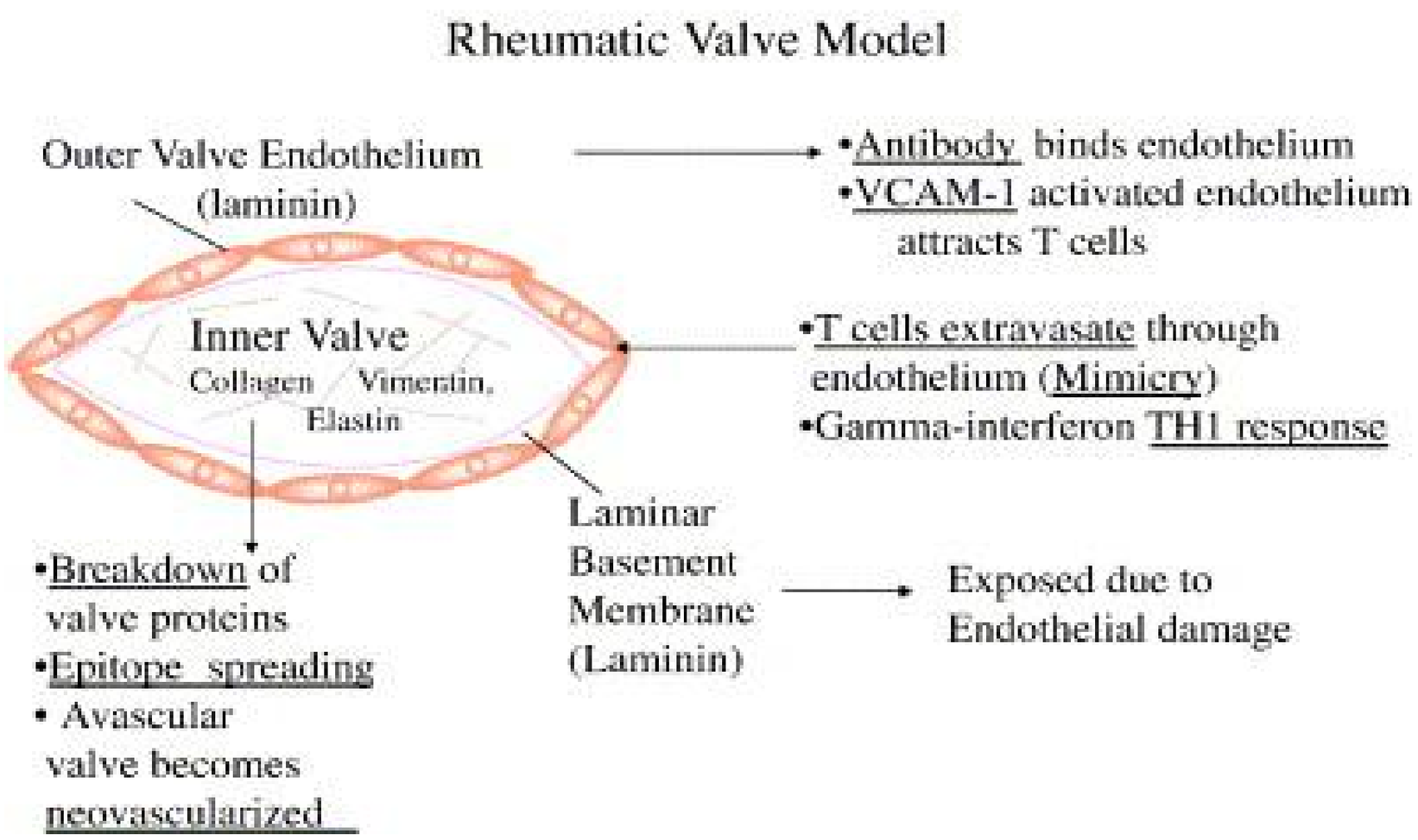


Diagram illustrating the process of initial mimicry which leads to **granuloma formation, gamma interferon production and scarring in the valve**. After the initial process has developed inflammation in the valve, other proteins in the valve may then be recognized by the immune system leading potentially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

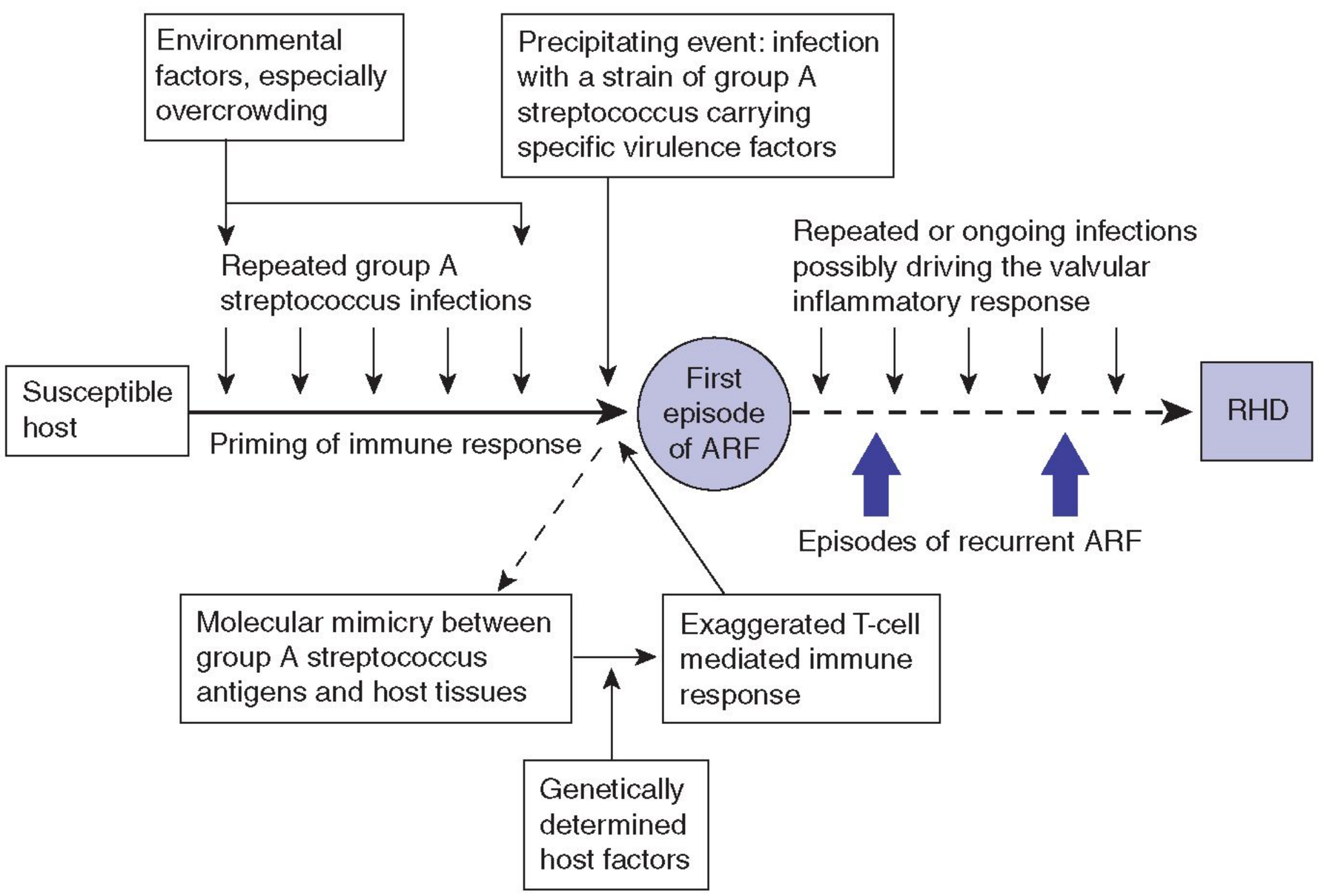
Pathophysiology

- 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**.

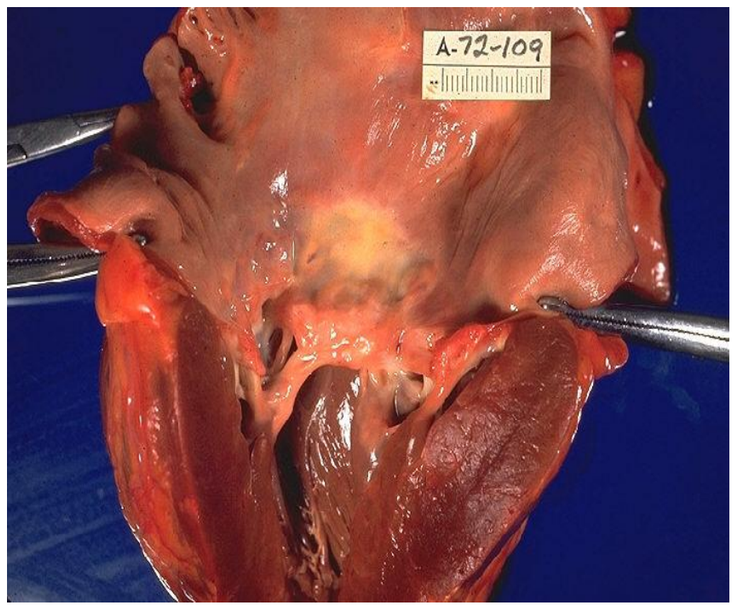
- *this situation is called the molecular mimicry which is the similarity between foreign antigen and self antigen



Clinical Presentation

Heart:

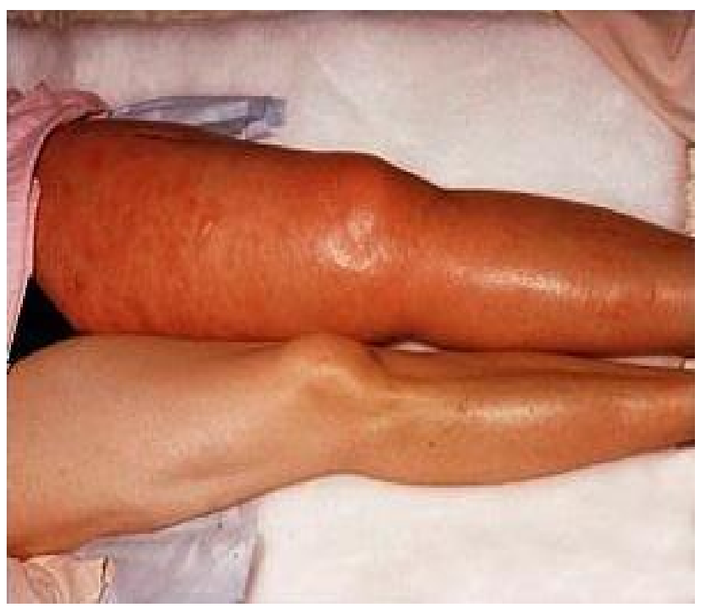
- Up to 60% of patients with ARF progress to Rheumatic Heart Disease (RHD).
- The endocardium, pericardium, or myocardium may be affected (**pancarditis**).
- Valvular damage is the hallmark of rheumatic carditis.



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.

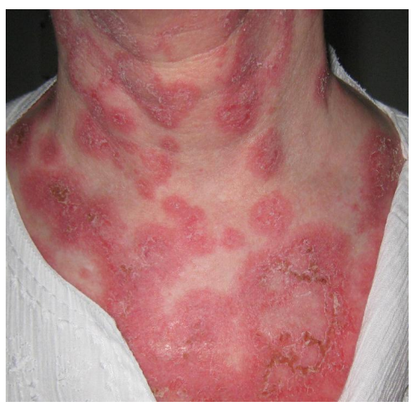
Joints (arthritis):

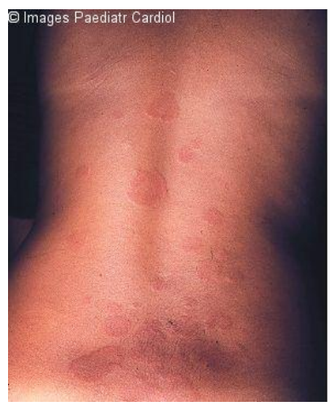
- This is usually polyarthritis, sometimes **flitting** (الانتفاخ يصيب اكثر مَنْ مفصل وينتقل من مفصل لآخر) from joint to joint (migratory), affecting the larger joints more than the smaller ones.
- Swelling, redness and tenderness are the common findings and occasionally joint effusions.
- Inflamed **Keen Joint.**



Skin (Erythema Marginatum):

- **Skin lesions**: The classical **erythema marginatum** lesions with prominent margins slightly Raised.



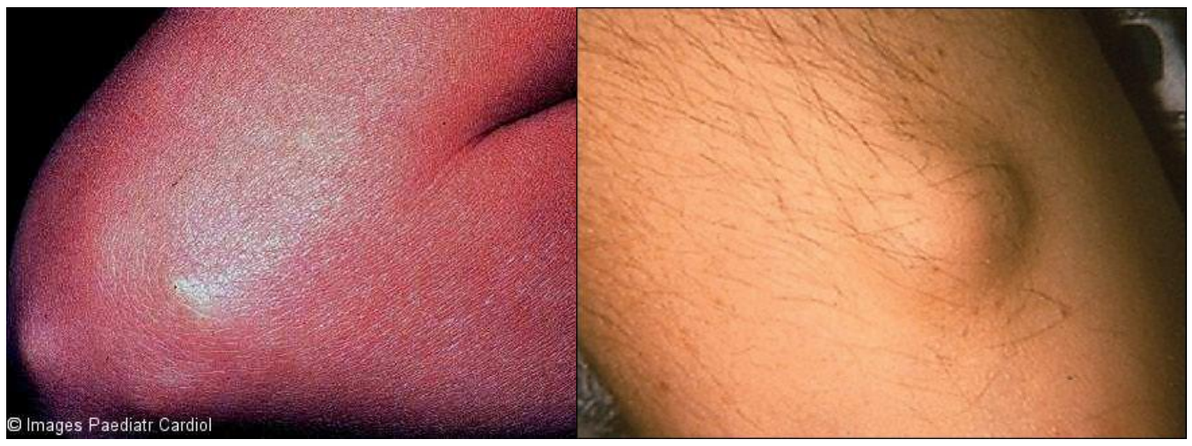


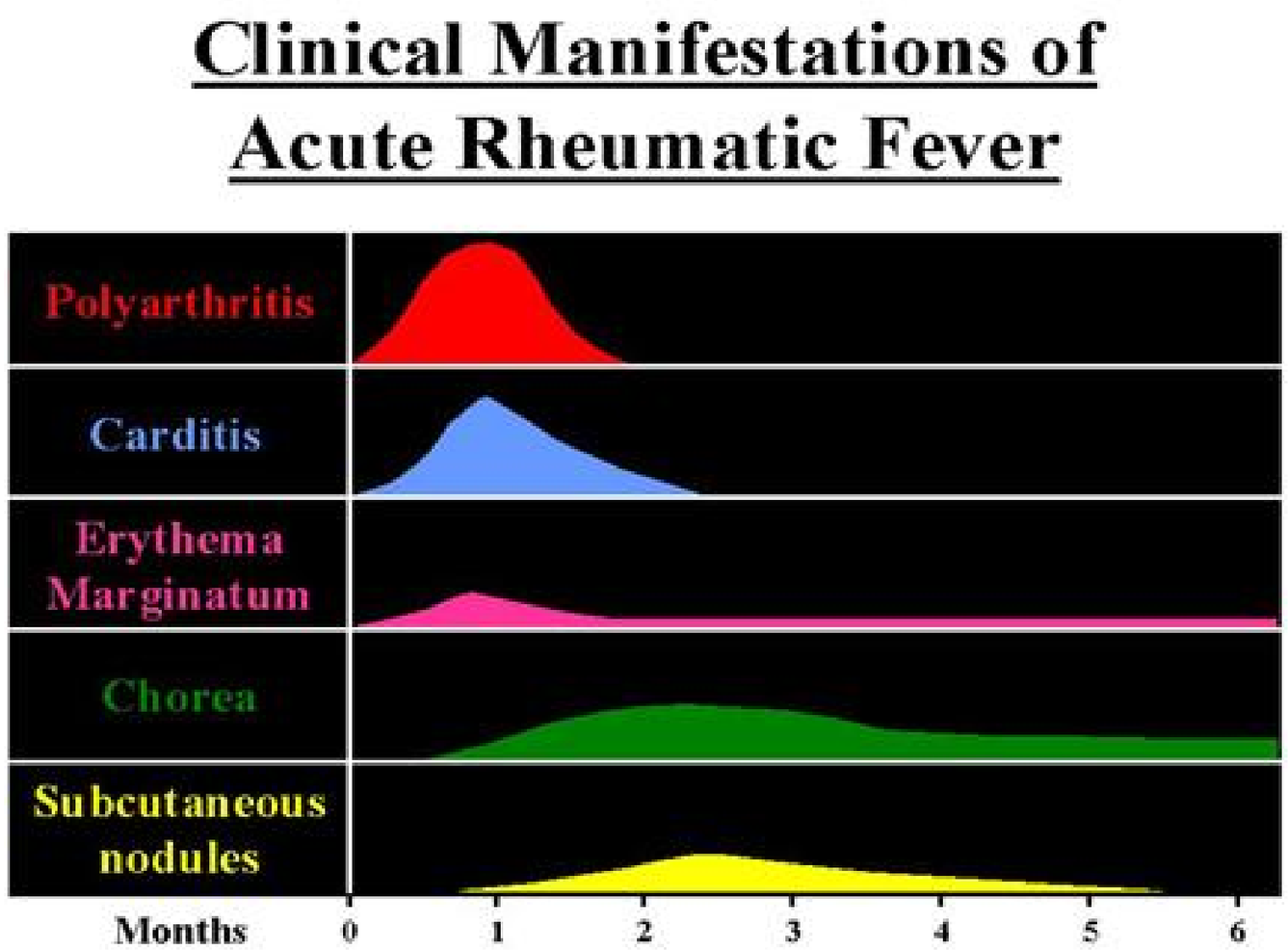
Central nervous system (chorea):

- **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 (كتلة أو نتوء) 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.





Investigation of Rheumatic Fever

Anti-streptolysin O (ASO) titer

The 2 most used

- 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

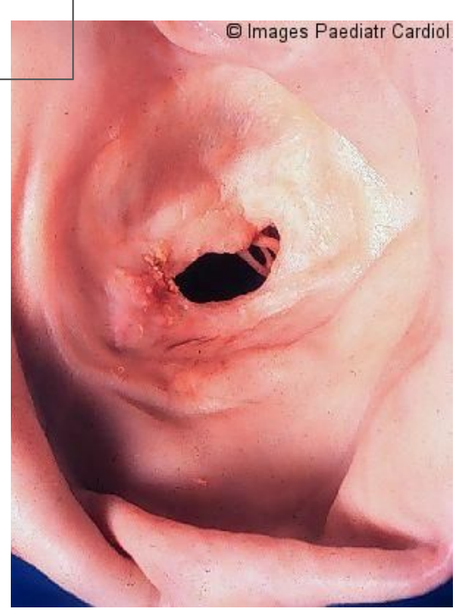
Subsequent attacks:

- 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).

As we said before the avascular valves become vascular which brings blood with fibrin and collagen and causes fibrosis. Fibrosis makes the valve stiff and unable to move the blood in a proper way.



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 Messages

- 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.

Useful videos:

Rheumatic fever:

General Overview

Sydenham's Chorea

Endocarditis:

General Overview

Animation

Valvular Heart Diseases:

Aortic Valve Diseases

Mitral Valve Diseases

Prolapse of Mitral valve this can happen as primary Myxomatous degeneration called floppy valve

https://www.youtube.com/watch?v=AHBzu5zhFuA

MCQs:

1 – in Rheumatic Heart Disease only CMI is important:

A) true B) false

2 – help in Adherence of Streptococcus pyogenes to host cells:

A)Hyaluronic acid capsule B)Peptidases C)HLA-DR7 D) m proteins

3 – Camouflages the bacterium and hide it:

A) Pyrogenic toxins B)Hyaluronic acid capsule C) m protein D) Streptolysins

4 – Streptokinase's rule in RHD :

A) Degrades proteins involved in immune response B) Lyse RBC, WBC C) Dissolve blood clots

5– which type of hypersensitivity in Rheumatic fever:

A) I B) II C) III D) IV

6 - Tricuspid valve is the most commonly affected in RHD:

A) true B) false

1-B
2-D
3-B
4-C
5-B
6-B

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