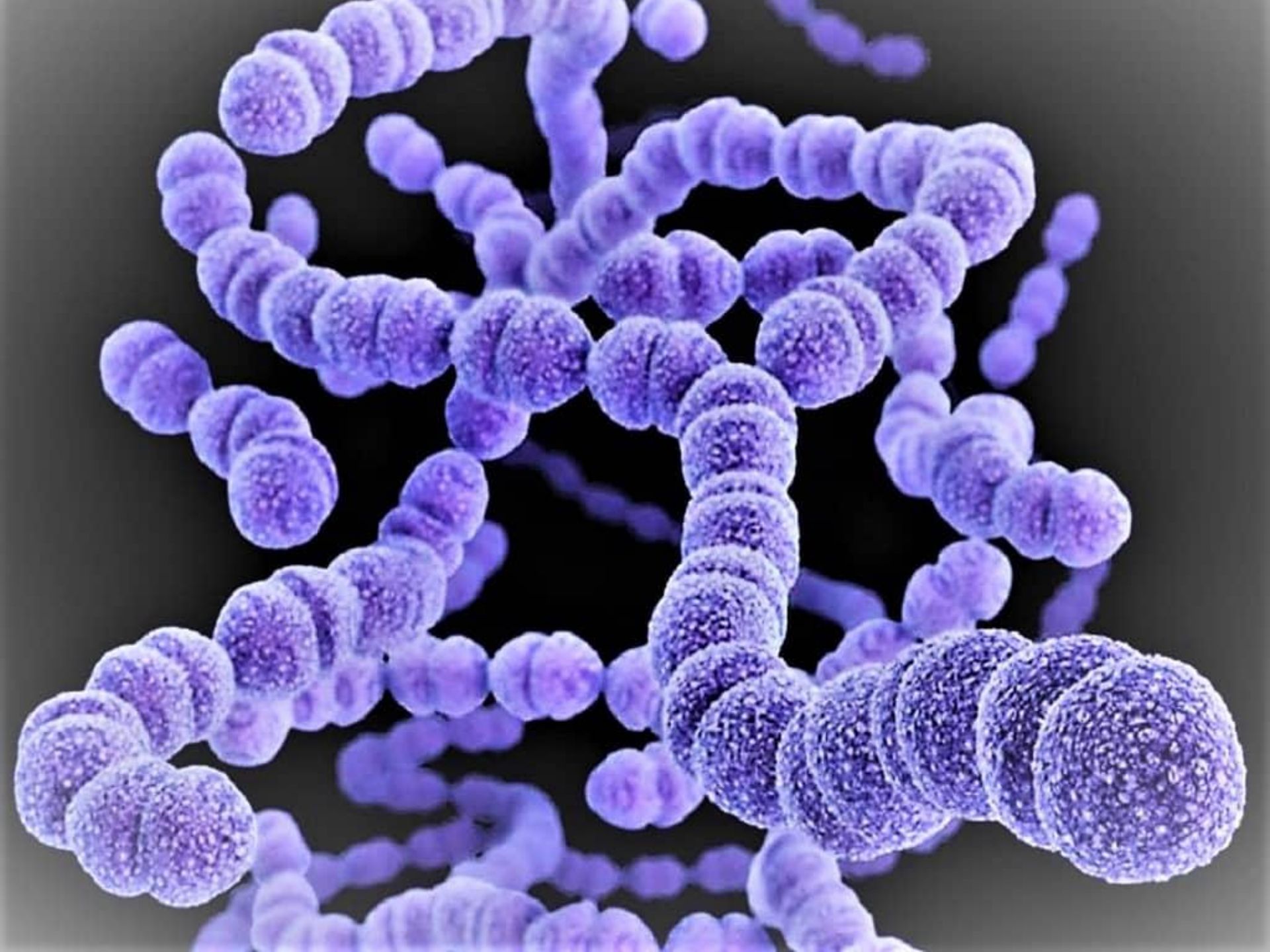
Rheumatic fever

Learning objectives

- Describe key structural features,
- virulence factors,
- modes of pathogenesis and
- diagnosis of Streptococcus pyogenes
- Explain etiology, pathogenesis, clinical
- features, diagnosis, and complications of Rheumatic Fever.

Structural features

- ***Streptococcus pyogenes*** is a species of Gram-positive,
- Aerotolerant bacterium in the genus *Streptococcus*.
- These bacteria are extracellular, non-motile and non-sporing cocci.
  - Group A streptococci when grown on blood agar typically produces small zones of beta-hemolysis, a complete destruction of red blood cells.
  - It is thus also called group A (beta-hemolytic) streptococcus (GABHS).
  - Streptococci are round bacteria.
  - Streptococci are catalase-negative



Mode of spread

- Respiratory droplets.
- Hand contact with nasal discharge and skin contact with impetigo lesions.
- The pathogen can also be found in its carrier state (anus, vagina, skin, pharynx)
- Can also be spread from cattle to humans through raw milk and contaminated foods (salads, milk, eggs)

- in 1946, Lancefield described the serologic classification of *S. pyogenes* isolates based on their surface T-antigen
- Four of the 20 T-antigens have been revealed to be pili, which are used by bacteria to attach to host cells. As in 2016, a total of 120 M proteins are identified.

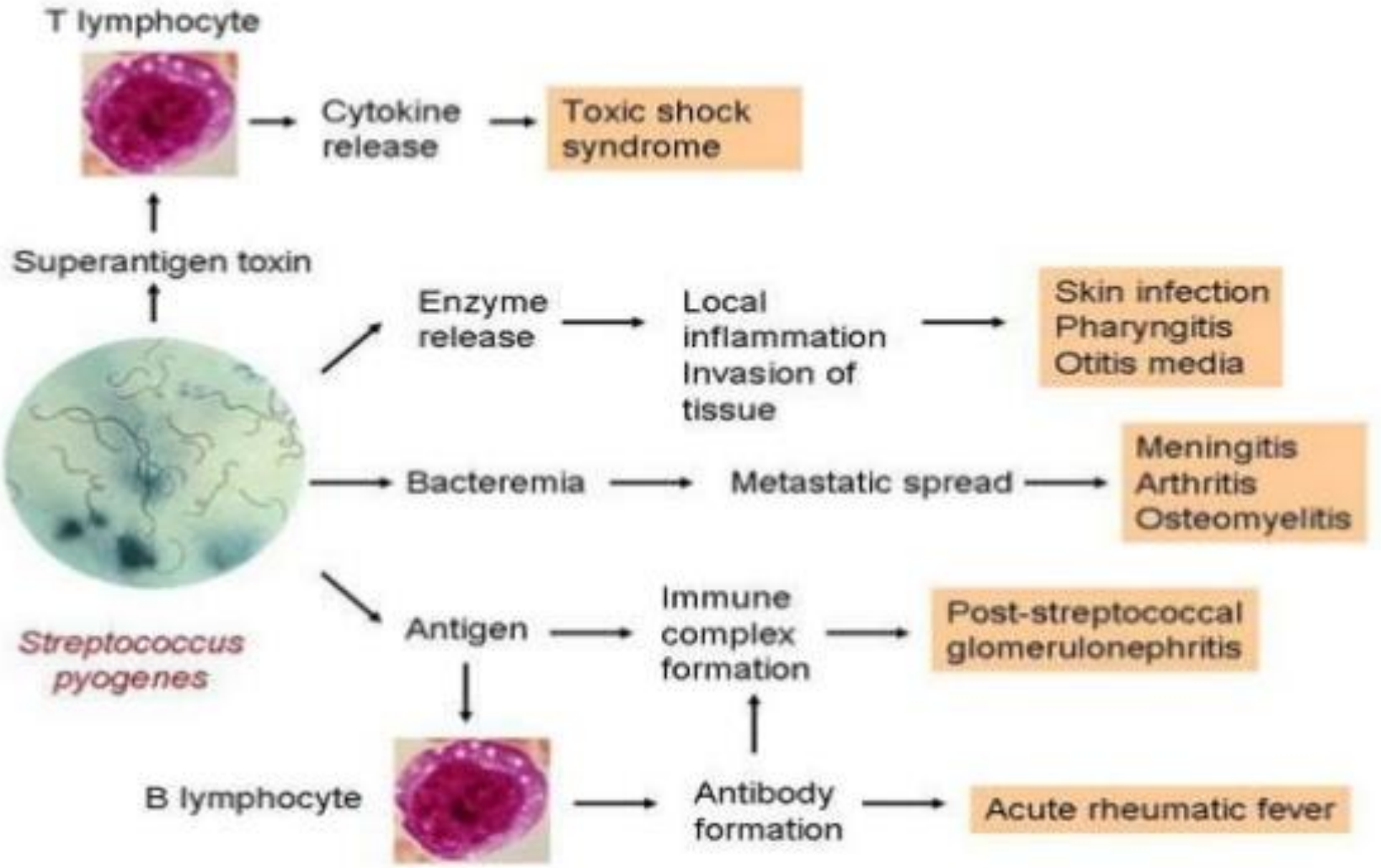
Virulence

- A carbohydrate-based bacterial capsule composed of hyaluronic acid surrounds the bacterium, protecting it from phagocytosis by neutrophils. In addition, the capsule and several factors embedded in the cell wall, including M protein, lipoteichoic acid, and protein F facilitate attachment to various host cells. M protein also inhibits opsonization by the alternative complement pathway by binding to host complement regulators or in some types to fibrinogen.

Virulence factor and Pathogenesis

- S. pyogenes cell wall has branched polymers which sometimes contain M protein, a virulence factor that is highly antigenic.
- The antibodies which the immune system of host generates against the M protein may cross-react with heart muscle cell protein myosin, heart muscle glycogen and smooth muscle cells of arteries, inducing cytokine release thus causing damage.

Pathogenicity



Structural components of *S. pyogenes* that cross react with human tissues

Structural components of *S. pyogenes*	Human tissue with which it cross reacts
Capsular hyaluronic acid	Synovial fluid
Cell wall protein	Myocardium
Cell wall carbohydrtes	Cardiac valves
Cytoplasmic membrane antigens	Vascular intima
Peptidoglycans	Skin antigens

Toxins and enzymes

1. **Hemolysins (Streptolysins)**
2. **Erythrogenic toxin**
3. **Streptokinase (Fibrinolysin)**
4. **Deoxyribonucleases (Streptodornase, DNAase)**
5. **Hyaluronidase**

Diagnosis

- **Gram staining** (Purple color cocci in chain arrangement)
- **Culture** (Culture on blood agar)

  Addition of bacitracin in inoculum: *S pyogenes* are sensitive to bacitracin

  Colonial appearance: Grayish white, transparent to translucent, matte or glossy; smooth; flatn;large zone of beta hemolysisn

  Catalase negative, oxidase negative ,

- **Antigen detection tests**

CONTD

- **Serologic tests**

  Detection of antibody titer after 3 to 4 weeks after exposure to organism

  Antibodies include ASO, anti-DNase B, anti-hyaluronidase, antistreptokinase, anti- M type specific antibodies

  Anti Streptolysin O (ASO) is most widely used.

Rheumatic fever

- Rheumatic fever (RF) is an acute, immunologically mediated, multisystem inflammatory disease classically occurring a few weeks after an episode of group A streptococcal pharyngitis; occasionally, RF can follow streptococcal infections at other sites, such as the skin.

ETIOLOGY

- Acute rheumatic fever is a systemic disease of childhood, often recurrent that follows group A beta hemolytic streptococcal infection.
- It is a delayed non-suppurative sequelae .
- It is a diffuse inflammatory disease of connective tissue, primarily involving heart ,blood vessels ,joints, subcut.tissue and CNS.

Pathogenesis

Acute rheumatic fever results from host immune responses to group A streptococcal antigens that cross-react with host proteins.

Antigen- presenting cells present the bacterial antigen to CD4+T cells which differentiate into helper T2 cells. Helper T2 cells subsequently activate the B cells to become plasma cells and induce the production of antibodies against the cell wall of Streptococcus.

. In particular, antibodies and CD4+ T cells directed against streptococcal M proteins can also in some cases recognize cardiac self-antigens .

- Antibody binding can activate complement, as well as recruit Fc-receptor bearing cells (neutrophils and macrophages); cytokine production by the stimulated T cells leads to macrophage activation Damage to heart tissue may thus be caused by a combination of antibody- and T cell-mediated reactions.

Clinical features

RF is characterized by a constellation of findings:

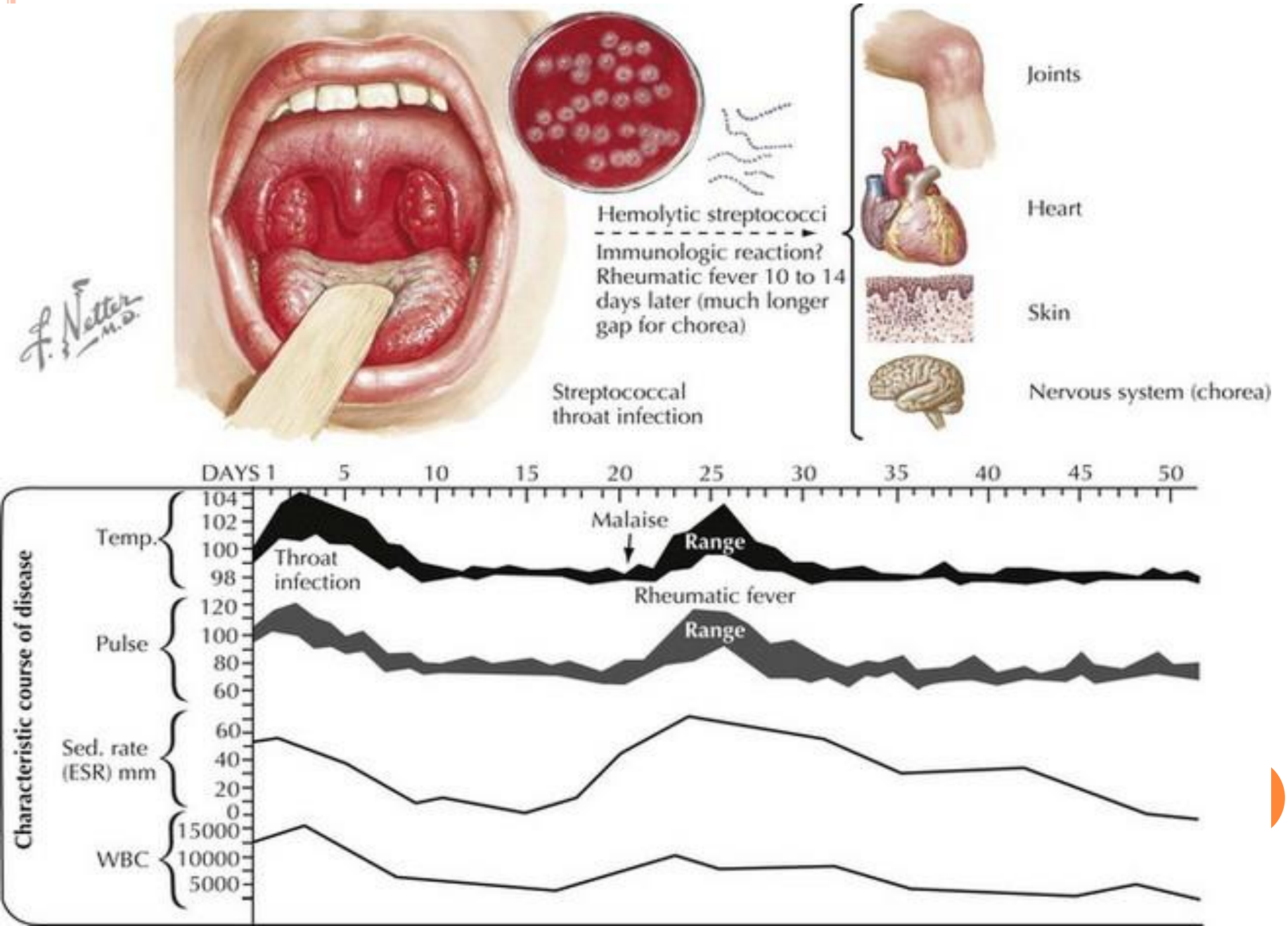
(1) Migratory polyarthritis of the large joints,

(2) Pancarditis,

(3) Subcutaneous nodules,

(4) Erythema marginatum of the skin,

(5) Sydenham chorea, a neurologic disorder with involuntary rapid, purposeless movements.


Hemolytic streptococci
Immunologic reaction?
Rheumatic fever 10 to 14 days later (much longer gap for chorea)
Streptococcal throat infection
Joints
Heart
Skin
Nervous system (chorea)
DAYS 1 5 10 15 20 25 30 35 40 45 50
Characteristic course of disease
Temp.
104
102
100
98
Throat infection
Malaise
Range
Rheumatic fever
Pulse
120
100
80
60
Range
Sed. rate (ESR) mm
60
40
20
0
WBC
15000
10000
5000

Clinical Features

Arthritis

- Migratory polyarthritis, involving major joints
- Commonly involved joints-knee, ankle,elbow & wrist
- Occur in 80%,involved joints are exquisitely tender
- **In children below 5 yrs arthritis usually mild but carditis more prominent**
- Arthritis do not progress to chronic disease

Clinical Features (Contd)

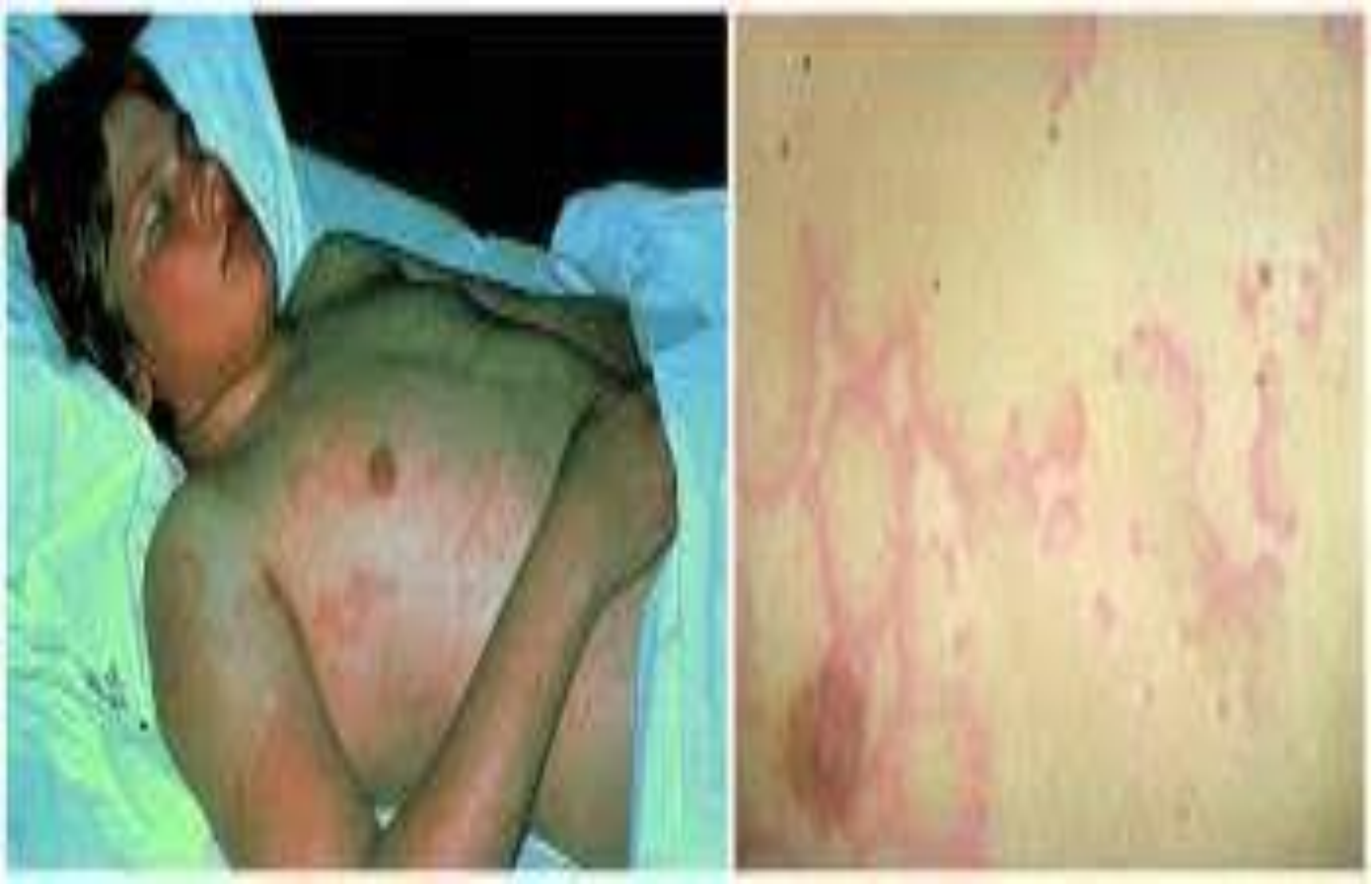
Carditis

- Manifest as **pancarditis**(endocarditis, myocarditis and pericarditis),occur in 40-50% of cases
- Carditis is the only manifestation of rheumatic fever that leaves a sequelae & permanent damage to the organ
- Valvulitis occur in acute phase.
- Chronic phase- fibrosis,calcification & stenosis of heart valves.

Clinical Features (Contd)

Erythema Marginatum

- Occur in <5%.
- Unique, transient lesions of 1-2 inches in size
- Pale center with red irregular margin
- More on trunks & limbs & non-itchy
- Worsens with application of heat
- Often associated with chronic carditis.



Clinical Features (Contd)

Subcutaneous nodules

- Occur in 10%
- Painless ,pea-sized, palpable nodules
- Mainly over extensor surfaces of joints, spine, scapulae & scalp
- Associated with strong seropositivity
- Always associated with severe carditis

Laboratory Findings

- High ESR
- Anemia, leucocytosis
- Elevated C-reactive protien
- ASO titre >200. (Peak value attained at 3 weeks, then comes down to normal by 6 weeks)
- Anti-DNAse B test
- Throat culture-GABH streptococci
- ECG- prolonged PR interval
- Echo - valve edema,mitral regurgitation, LA & LV dilatation,pericardial effusion,decreased contractility

Diagnosis

- Rheumatic fever is mainly a clinical diagnosis
- No single diagnostic sign or specific laboratory test available for diagnosis
- Diagnosis based on **MODIFIED JONES CRITERIA**

DIAGNOSTIC EVALUATIONS

A diagnosis of rheumatic heart disease is made after confirming antecedent rheumatic fever.

The modified Jones criteria (revised in 1992) provide guidelines for the diagnosis of rheumatic fever.

JONES CRITERIA

- 2 major or
- 1 major and 2 minor

Jones' criteria for the diagnosis of Rheumatic fever

Major manifestations : Carditis, Polyarthritis, Chorea, Erythema marginatum, Subcutaneous nodules

Minor manifestations

a) Clinical findings, Previous rheumatic fever or rheumatic heart disease, Arthralgia , Fever associated with weakness, malaise, weight loss and anorexia

Complications

- Involvement of the central nervous system may be manifested by meningoencephalitis, hyperpyrexia or psychotic symptoms.
- Respiratory system involvement may produce pleuritis and pneumonitis
- . Vascular lesions may produce coronary arteritis and aoritis.
- The abdominal manifestations may occur as a result of serous fibrinoid peritonitis

- Glomerulonephritis may occur simultaneously with rheumatic fever in 4.5 to 5 per cent of all cases.
- Subacute bacterial endocarditis may also be associated with an acute exacerbation of rheumatic fever.
- Congestive heart failure is a complication of severe carditis

- Thanks