# Infectious Diseases for Graduate Students

- Infection and disease for biologists begins with the microbe
- Infectious Diseases for physicians begins with a patient complaining of a constellation of symptoms – a syndrome.
- A syndrome can be caused by more than one microbial agent.
- Therefore Infectious diseases are usually first characterized by the dominant organ system which the patient's symptoms reveal by symptoms.

# An Example of a Syndrome –Respiratory Tract Infection

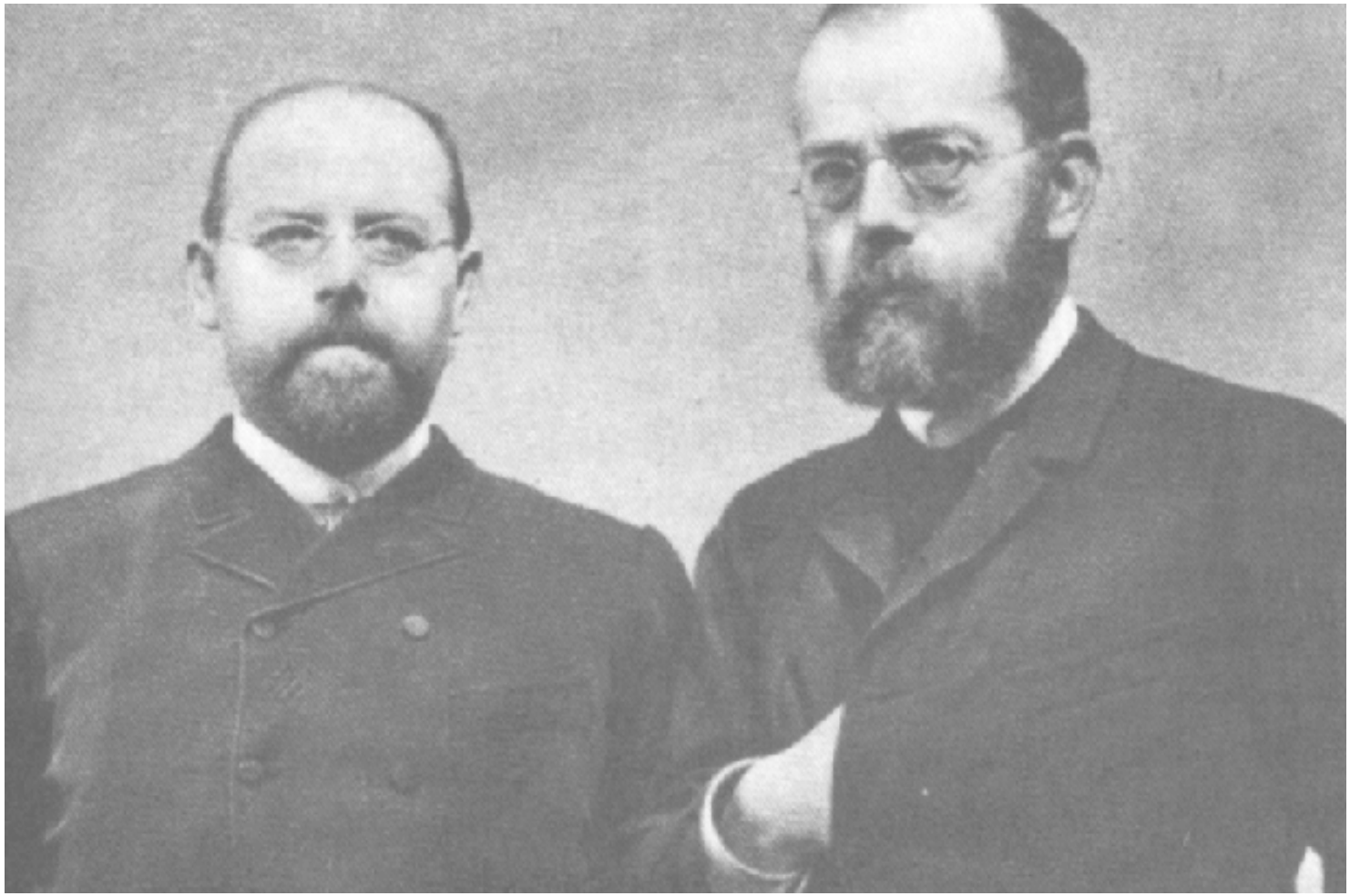
- Streptococcus pneumoniae is the most common cause of adult community-acquired pneumonia.
- The patient does not present with complaining of pneumococcal pneumonia.
- Rather, the patient complains of fever, cough, shortness of breath and chest pain , perhaps with chills.
- Similar symptoms can be caused by viral agents and any different bacterial agents, fungi and even large parasites.
- The differential diagnosis is made by and by careful attention to the patient's history coupled with physical and laboratory examination.

# Some Terms Used to Describe Infectious Diseases

- Infection is growth and reproduction of a microorganism on or within a host
- Disease is is the overt clinical damage done to the host by infection
- Pathology refers to the anatomic and tissue abnormalities induced by infection.
- Pathogenesis refers to the events induced by the microbe causing the pathology.
- A Pathogen is a microbe capable of causing disease.
- Virulence is a quantitative assessment of pathogenicity.

# Infectious Syndromes

- Skin and soft tissue
- Respiratory
  - Upper Respiratory
  - Lower Respiratory
- Gastrointestinal
- Urogenital Tract
- Nervous System
- Generalized or Systemic



Friedrich Loeffler and Robert Koch

**The Origin of Koch's Postulates**

"I therefore conclude that bacteria do not occur in the blood or tissues of healthy animals or humans."

"In order to prove that bacteria are the cause of traumatic infective diseases, it is necessary to show that bacteria are present without exception and that their number and distribution are such that the symptoms of the disease are fully explained."

***Koch, R. 1878 Untersuchungen über die Aetoiologie der Wundinfectionskrankheiten.***
***Vogel, Leipzig***

# Loeffler's Application of Koch's "Postulates"

- **If a disease [is] caused by a microoorganism, it is essential that three postulates be fulfilled:**
  - **1) The organism must be shown to be constantly present in characteristic form and arrangement in the diseased tissue.**
  - **2) The organism, which from its behavior appears to be responsible for the disease, must be isolated and grown in pure culture.**
  - **3) The pure culture must be shown to induce disease experimentally.**

# Current Textbook Statement of Koch's Postulates

- 1) The parasite occurs in every case of the disease in question and under circumstances which can account for the pathological changes and clinical course of the disease.
- 2) The parasite occurs in no other disease as a fortuitous and non-pathogenic parasite.
- 3) After being fully isolated from the body and repeatedly grown in pure culture, the parasite can induce the disease anew.

# Molecular Koch's Postulates

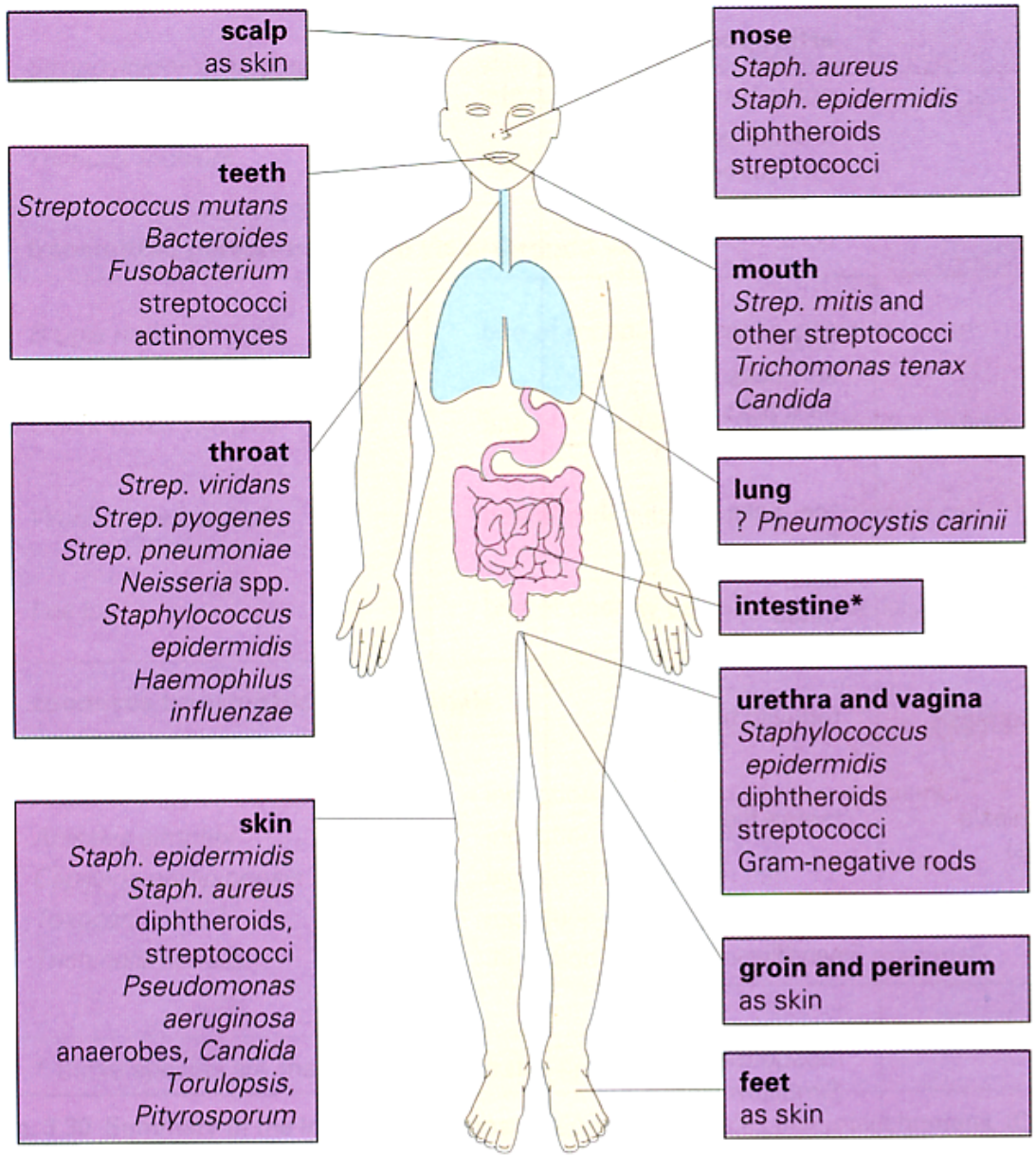
- 1) The phenotype or property under investigation should be associated with pathogenic members of a genus or pathogenic strains of a species.
- 2) Specific inactivation of the gene(s) associated with the suspected virulence trait should lead to a measurable loss in pathogenicity or virulence.
- 3) Reversion or allelic replacement of the mutated gene should lead to a restoration of pathogenicity.

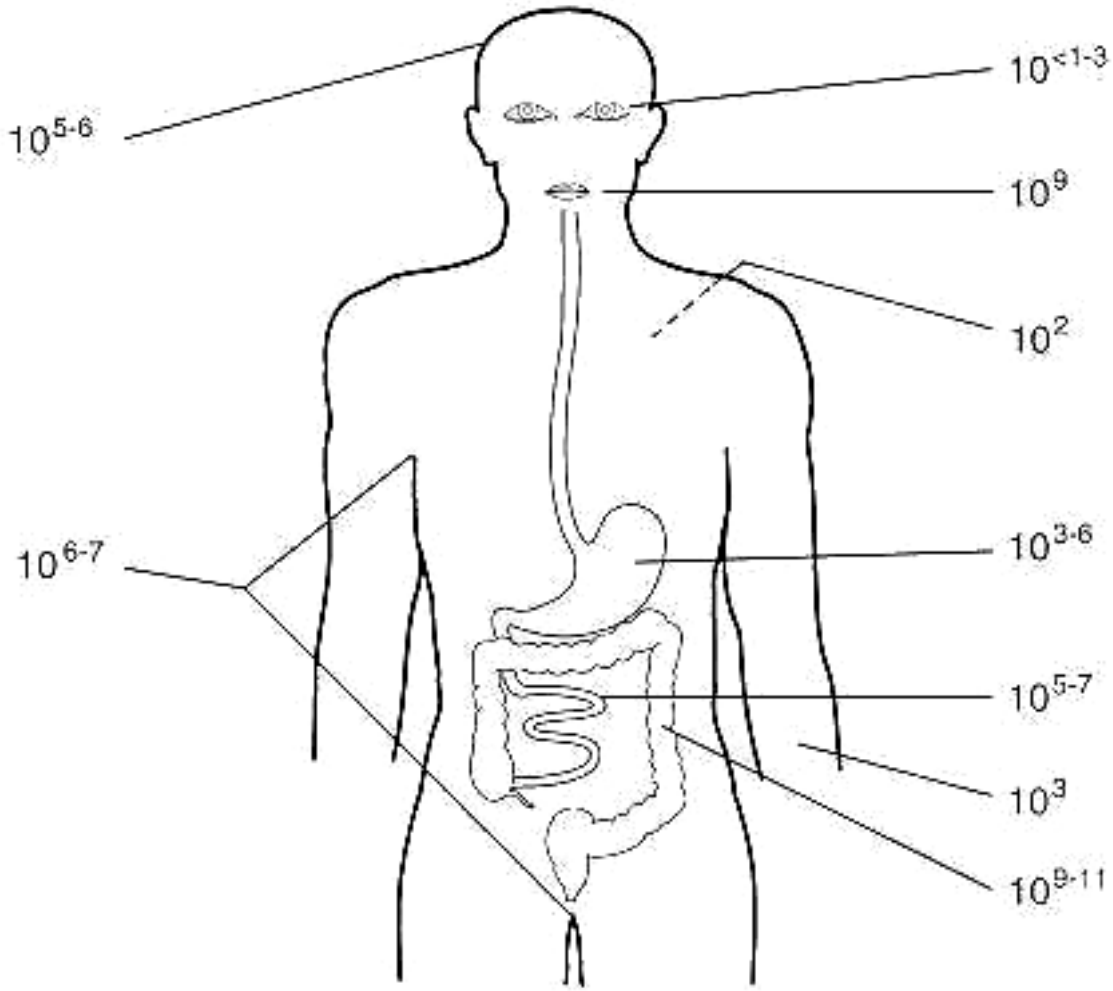
# Your First Assignment – To be handed in at the end of the course

What is your version of Koch's Postulates?

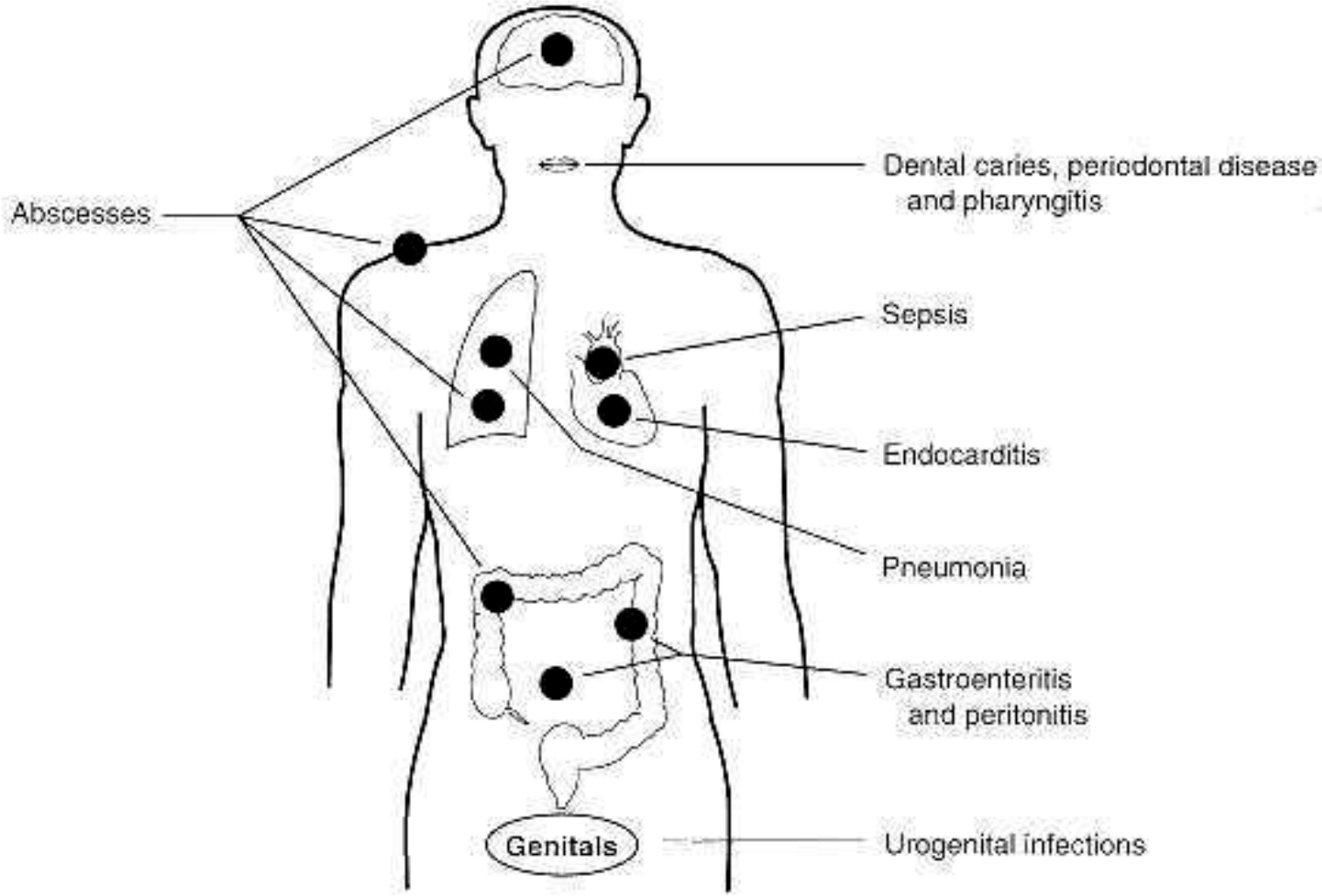
And Why?

# One Key to Understanding Medical Microbiology is to Understand the Normal Flora


**scalp**
as skin
**teeth**
*Streptococcus mutans*
*Bacteroides*
*Fusobacterium*
streptococci
actinomyces
**throat**
*Strep. viridans*
*Strep. pyogenes*
*Strep. pneumoniae*
*Neisseria* spp.
*Staphylococcus epidermidis*
*Haemophilus influenzae*
**skin**
*Staph. epidermidis*
*Staph. aureus*
diphtheroids,
streptococci
*Pseudomonas aeruginosa*
anaerobes, *Candida*
*Torulopsis,*
*Pityrosporum*
**nose**
*Staph. aureus*
*Staph. epidermidis*
diphtheroids
streptococci
**mouth**
*Strep. mitis* and
other streptococci
*Trichomonas tenax*
*Candida*
**lung**
? *Pneumocystis carinii*
**intestine***
**urethra and vagina**
*Staphylococcus epidermidis*
diphtheroids
streptococci
Gram-negative rods
**groin and perineum**
as skin
**feet**
as skin

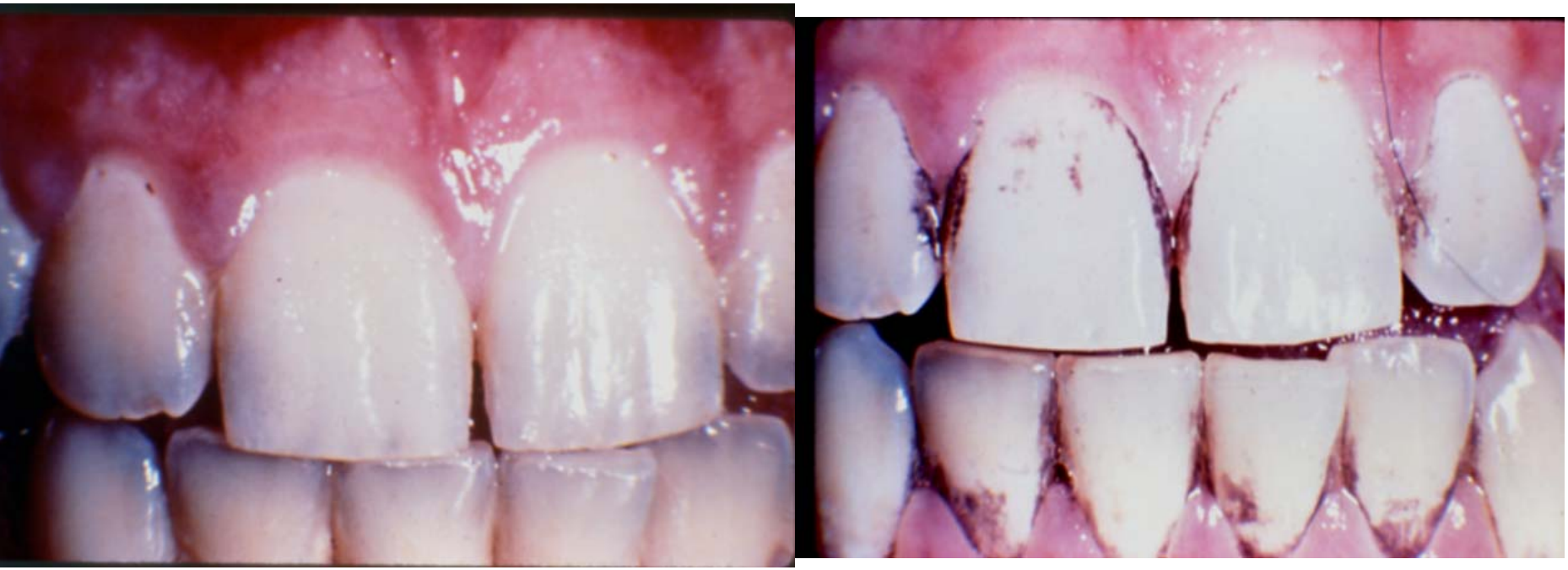



**Numbers of bacteria that colonize different parts of the body.** Numbers represent the number of organisms per gram of homogenized tissue or fluid or per square centimeter of skin surface




**Clinical conditions that may be caused by members of the normal flora.**

Many members of the Normal Flora are Anaerobic Species



Normal teeth just after brushing (left). A few minutes later after the addition of an oxidation-reduction (Eh) indicator (right). The dark discoloration denotes an anerobic environment

# *Staphylococcus aureus*

- Many neonates, most children and adults become transiently colonized by *S. aureus*.
- The organism is carried preferentially in the nasopharynx, occasionally on their skin and clothing and more rarely in the vagina, in the rectum and or perineal area.
- From these sites *S. aureus* can contaminate any site of the human body by intrapersonal transfer by aerosol and by direct contact.

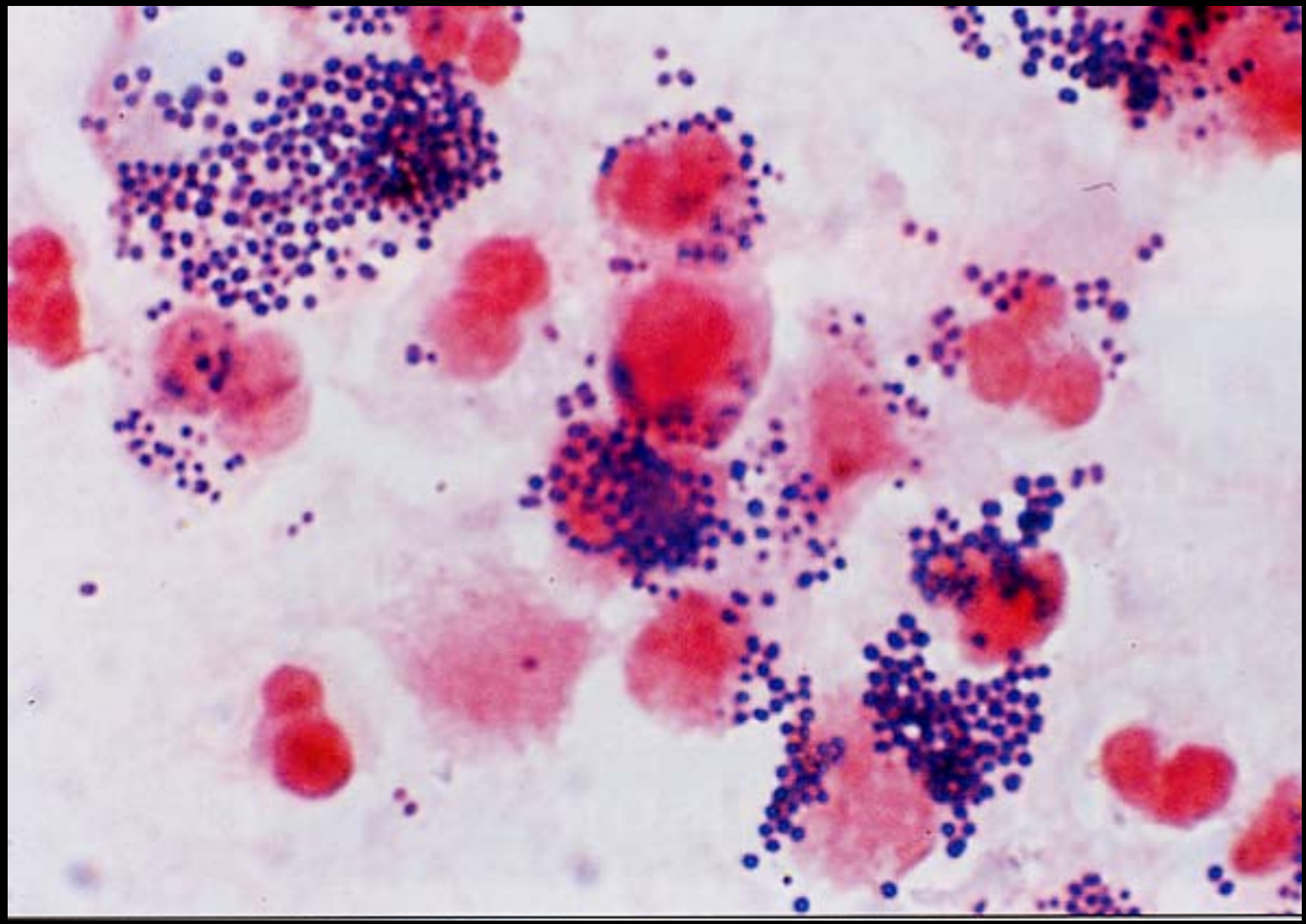
# *Staphylococcus aureus*

- The mucous membranes and the skin are very efficient barriers against local invasion.
- If the barrier is breached by trauma, surgery or other means (needles. Etc) the organisms gain access to the underlying tissue and creates a local abscess.
- The abscess is the hallmark of staphylococcal infection consisting of necrotic tissue, fibrin and a large number of live and dead PMN
- Toxin liberation o the skin and other organs can cause various types of rash, general symptoms as exemplified by TSS or diarrheal disease.

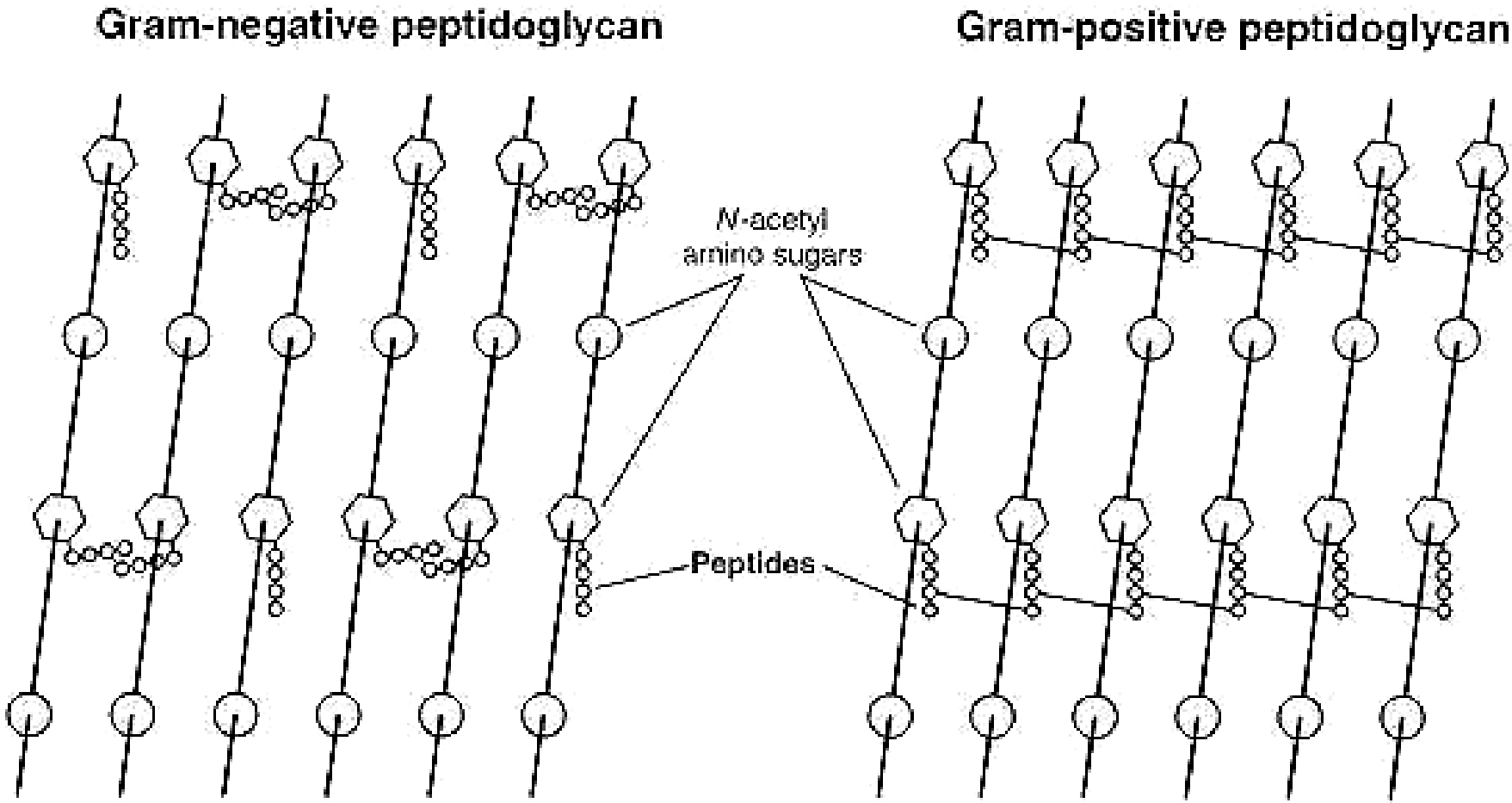
# *Staphylococcus aureus*

- Bacteria in local abscesses or multiplying at any site, can sometimes overcome local phagocytic defenses and gain acess to the lymph channels and blood stream.
- The resulting staphylococcal bacteria is a dreaded complication and can lead to deadly disease complications like pneumonia, endocarditis or osteomyelitis.
- Staphylococci are among the most robust microbes that infect humans. This and its propensity to develop antibiotic resistance establish this microbe as  a major human pathogen.`

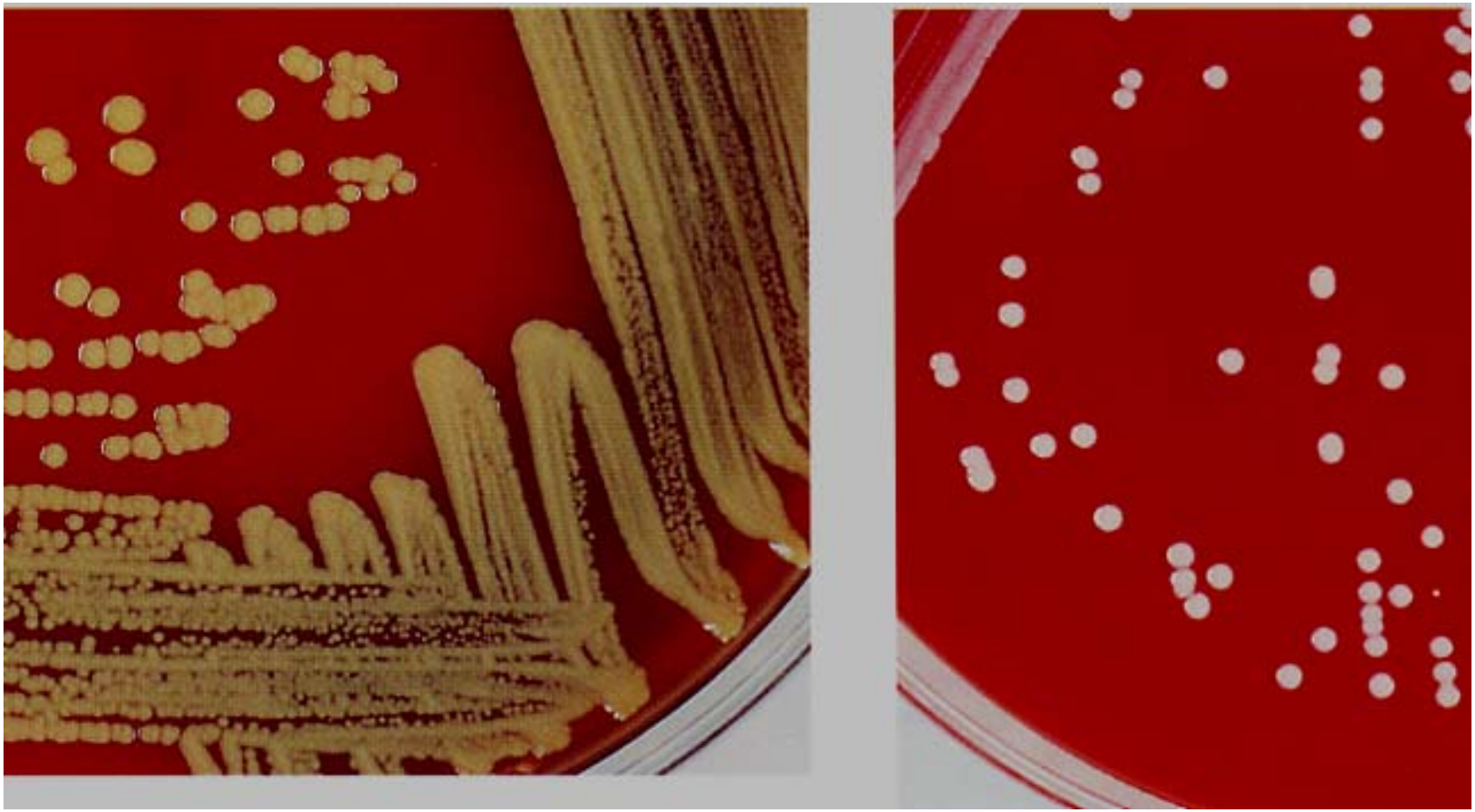
# The Bacteriology of the Staphylococci



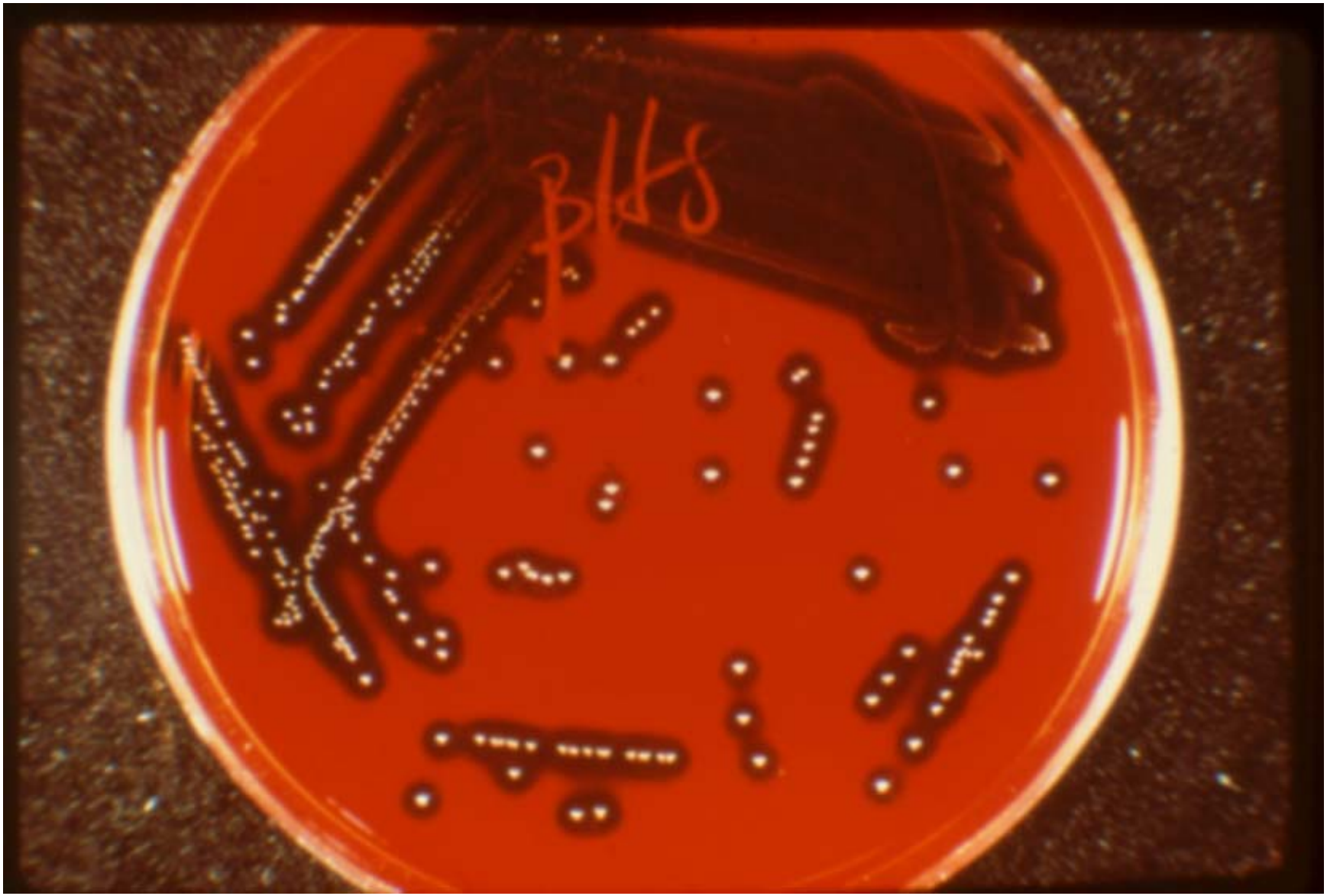
Gram stain of pus from postoperative abscess



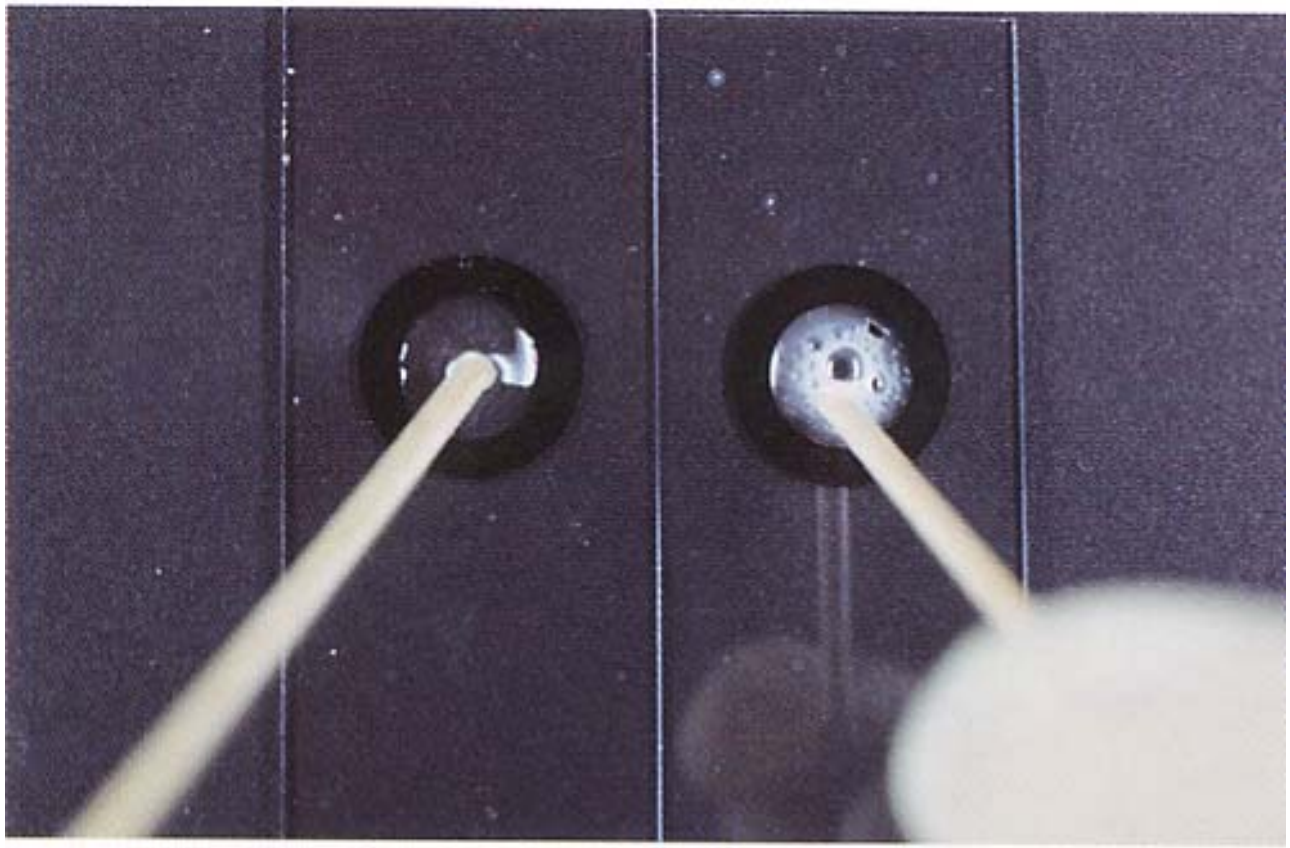

**Diagrammatic representation of peptidoglycan structures** with adjacent glycan strands cross-linked directly from the carboxyterminal D-alanine to the e-amino group of an adjacent tetrapeptide or through a peptide cross bridge ,N-acetylmuramic acid; N-acetylglucosamine



Typical colonies of *staphylococcus epidermidis* on right showing porcelin-white colonies as compared to *S. aureus* on the same medium (left) the golden appearance of the colonies. This clear distinction in colony color is not seen at all times.

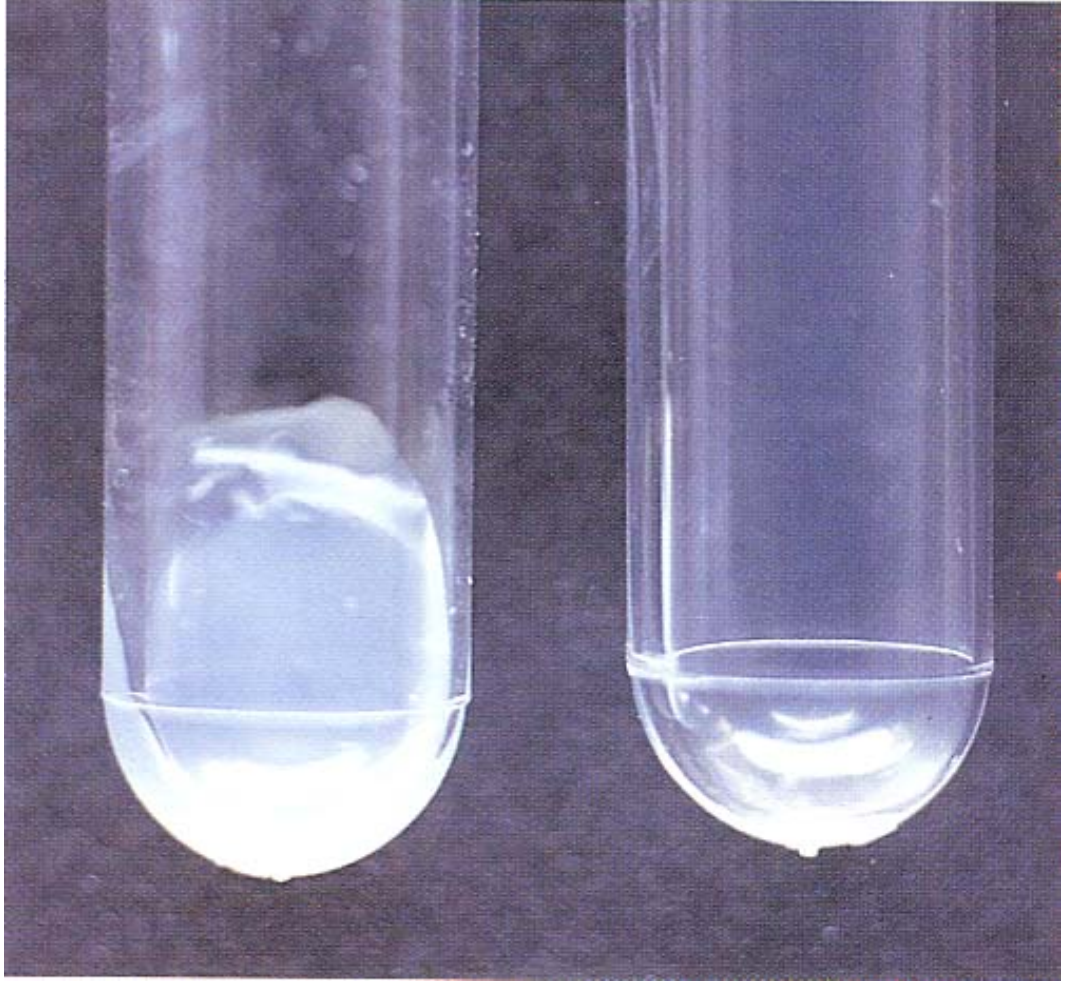



**Young colonies of *Staphylococcus aureus* showing beta hemolysis**

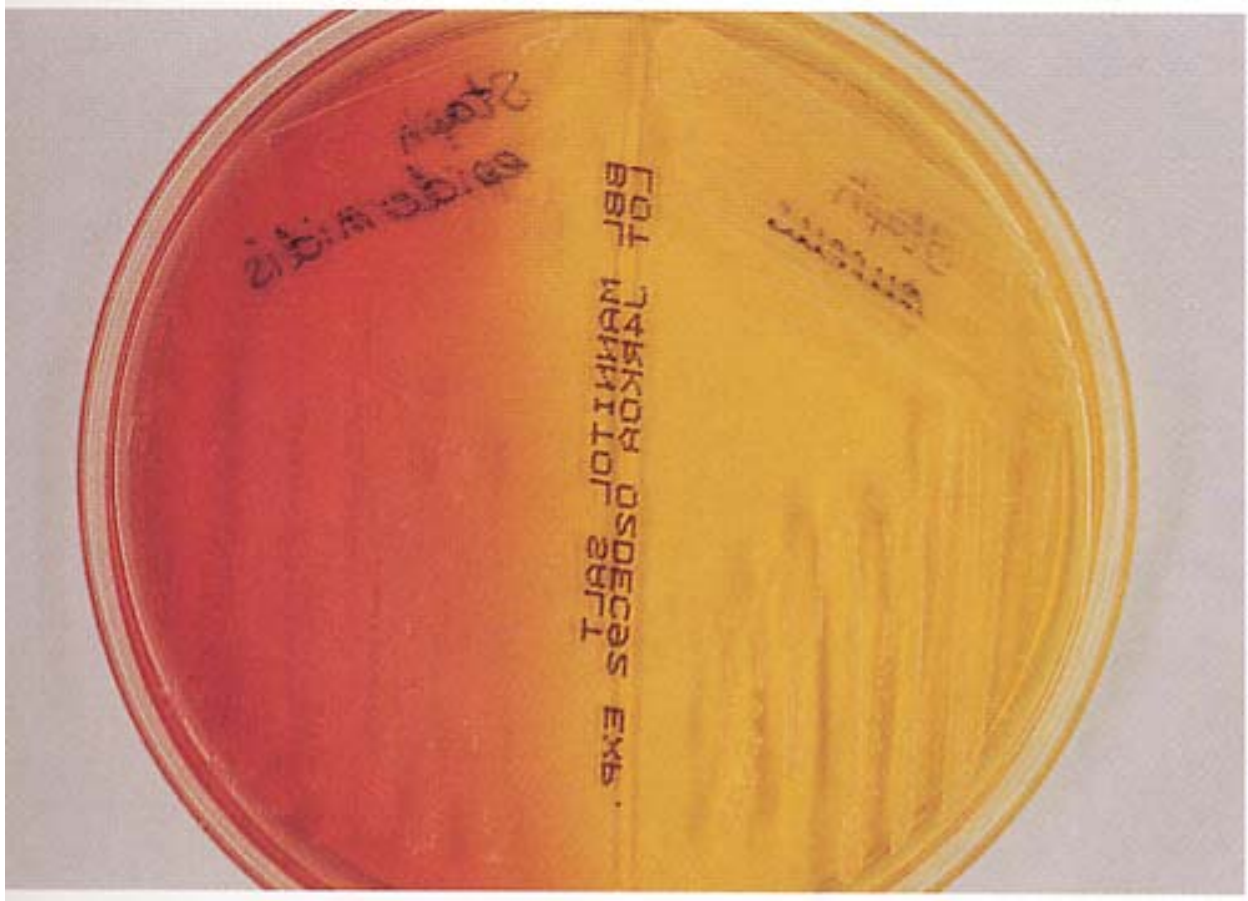


Staphylococci can be differentiated from other aerobic gram positive cocci by a positive catalase test. The test is performed by adding bacterial cells from a colony to a drop of 3% hydrogen peroxide. The appearance of bubbles (right) indicates the enzyme catalase while catalase negative bacteria give no reaction (left).

**Slide Coagulase test.**
The most important distinction among staphylococci is whether or not they produce the enzyme coagulase. *S. aureus* is the most common pathogen among the catalase positive gram positive cocci and is differentiated from other staphylococci by the coagulase test. Here the bacterial cells have been suspended in a drop of rabbit plasma. Coagulase bound to the cell wall acts on fibrinogen and causes the clumping of the bacteria (right). Coagulase is an important virulence factor of *S. aureus*.



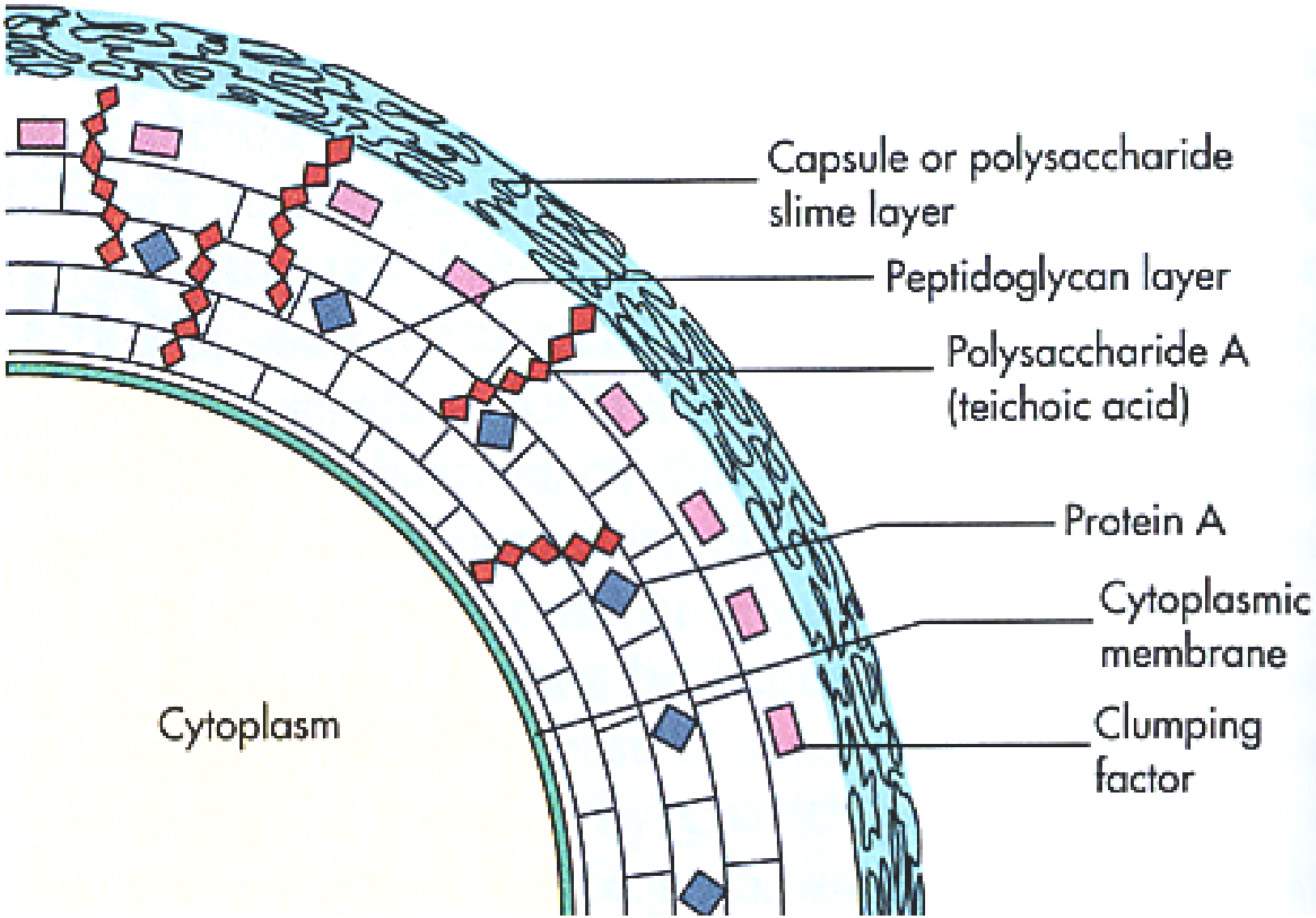
The tube coagulase test detects both free and cell bound coagulase of *S. aureus*. Bacteria are incubated in plasma for 2-4 hours and the tubes turned on their sides as illustrated. Free coagulase acts on prothrombin and fibrinogen in plasma and forms a fibrin clot (left). In many laboratories staphylococci are simply differentiated as coagulase positive or coagulase negative without speciation.



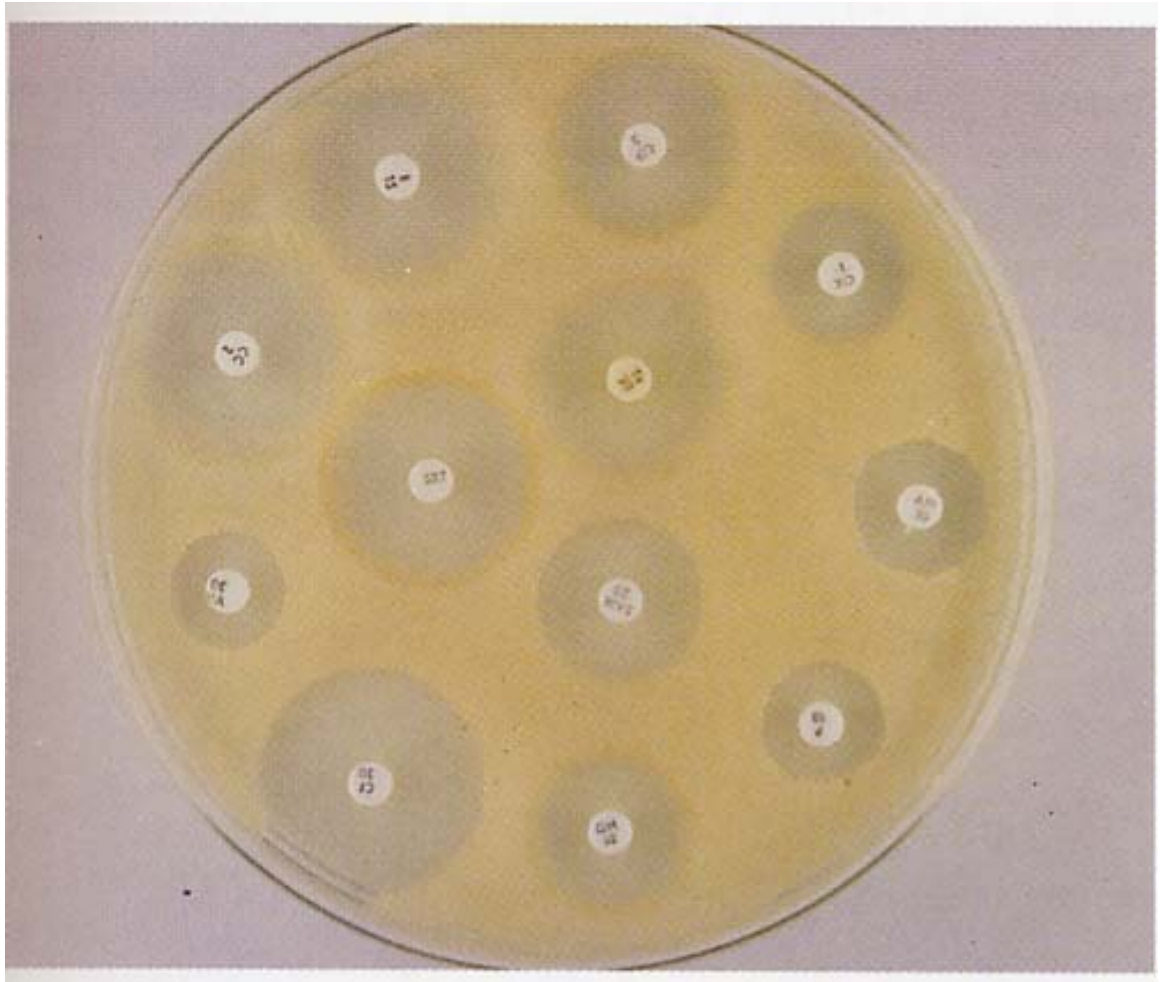
Growth on Mannitol-Salt agar differentiates *S. aureus* from other catalase positive gram positive cocci like *s. epidermidis*. *S. aureus* grows as shown here on an agar medium containing 7.5% NaCl which inhibits the growth of many other organisms. *S. aureus* also can ferment mannitol into acid detected here by the change in pH indicator from red to yellow. (right)

# Biochemical Classification of Staphylococci

| Species | Colony pigment | Staphylocoagulase | Clumping factor | Heat-stable nuclease | Alkaline phosphatase | Pyrrolidonyl arylamidase | Ornithine decarboxylase | Urease | β-Galactosidase | Acetoin production | Novobiocin resistance | Polymyxin B resistance | α-Trehalose | α-Mannitol |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *S. aureus* | d | + | + | + | + | − | (d) | d | − | + | − | + | + | + |
| *S. epidermidis* | − | − | − | − | + | + | − | + | − | + | − | + | + | − |
| *S. haemolyticus* | d | − | − | − | + | + | + | d | − | + | − | d | + | d |
| *S. lugdunensis* | d | (+) | − | − | + | + | + | − | − | + | − | − | + | − |
| *S. schleiferi* | − | + | − | + | + | + | + | − | (+) | + | − | − | d | − |
| *S. saprophyticus* | d | − | − | − | − | − | − | + | + | + | + | − | + | d |




***Staphylococcus aureus* cell wall**



Antimicrobial susceptibility testing of *S. aureus*.

Resistance to Antimicrobials particularly to β-lactam antibiotics is a major problem in the treatment of *S. aureus* and *S. epidermidis* disease.

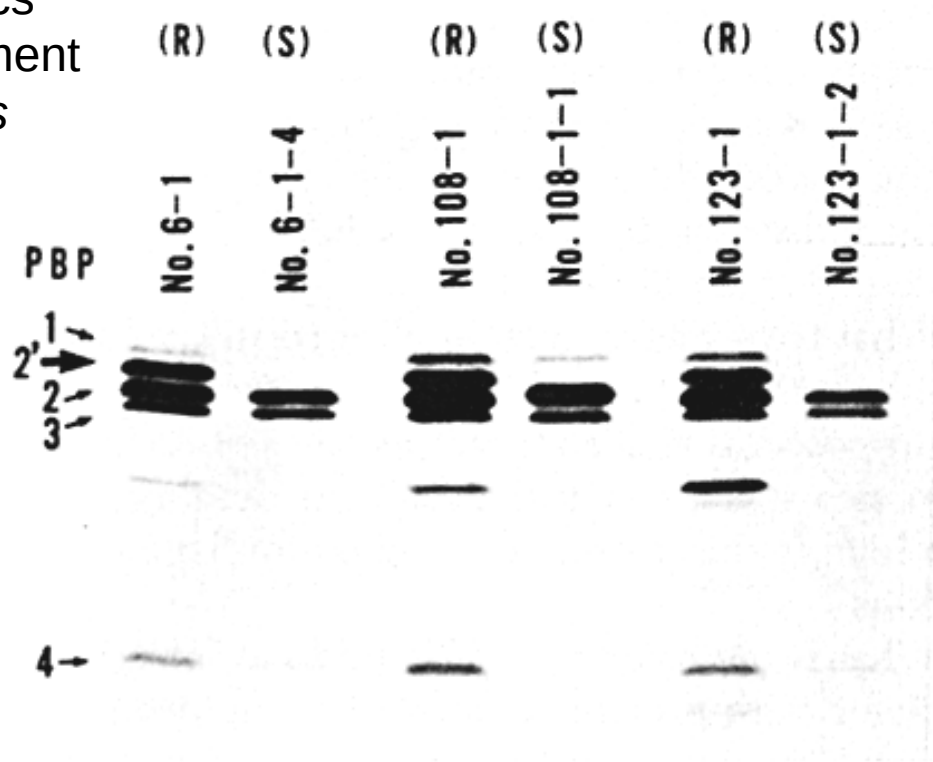
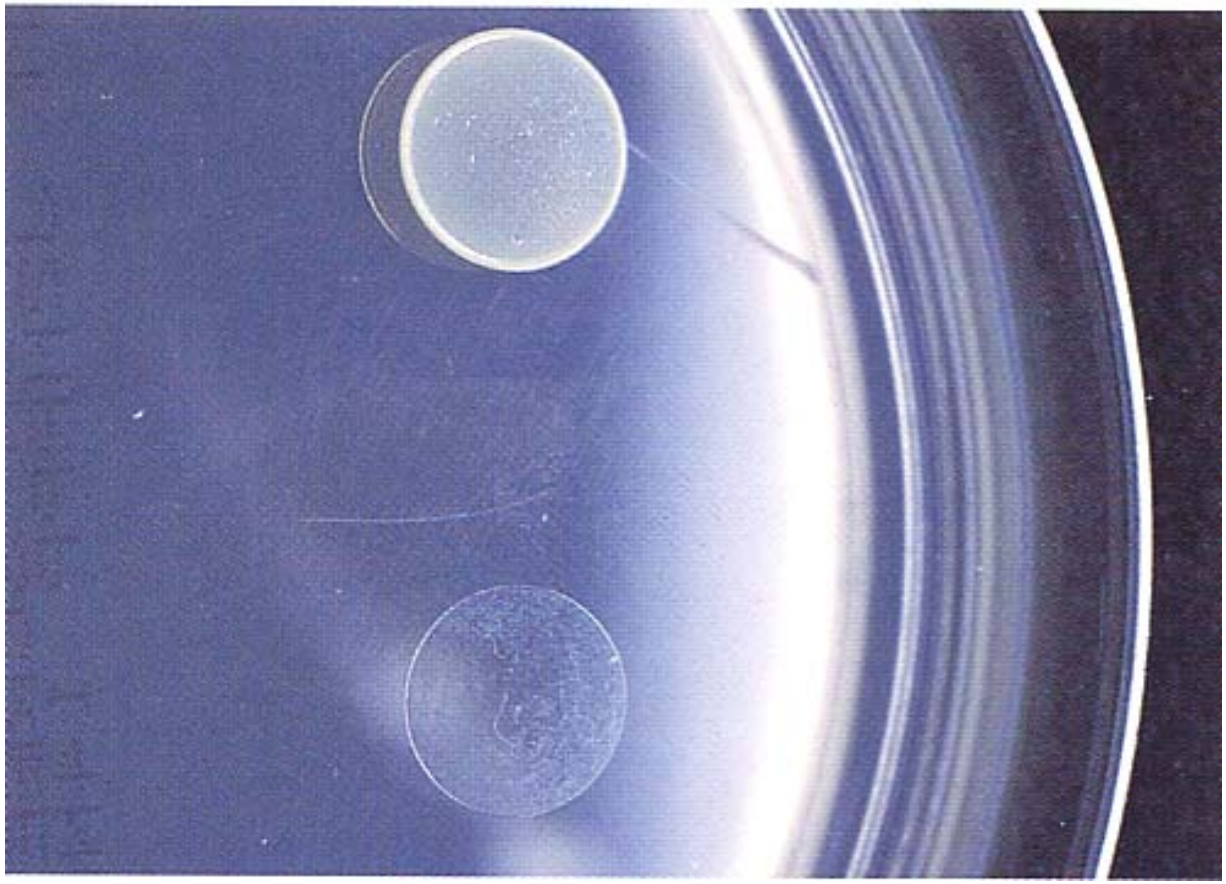


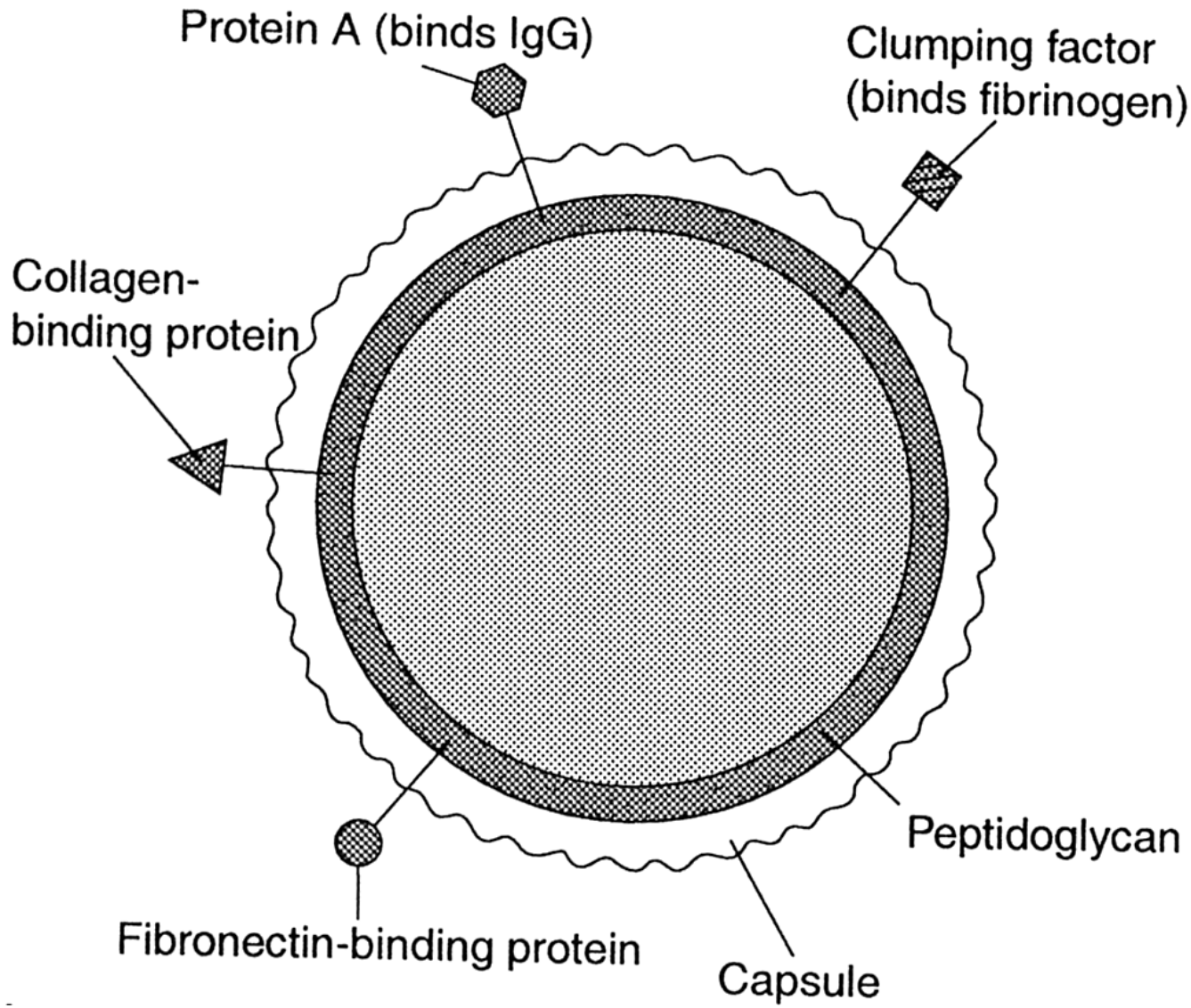

**FIGURE 22-10** Penicillin-binding protein profiles of methicillin-resistant *Staphylococcus aureus (6-1, 108-1, 123-1)* and methicillin-susceptible revertant strains *(6-1-4, 108-1-1, 123-1-2)*. Note that penicillin-binding protein 2′ is present in all methicillin-resistant strains and absent in all methicillin-susceptible strains. (From Utsui Y, Yokota T: *Antimicrob Agents Chemother* 28:397-403, 1985.)



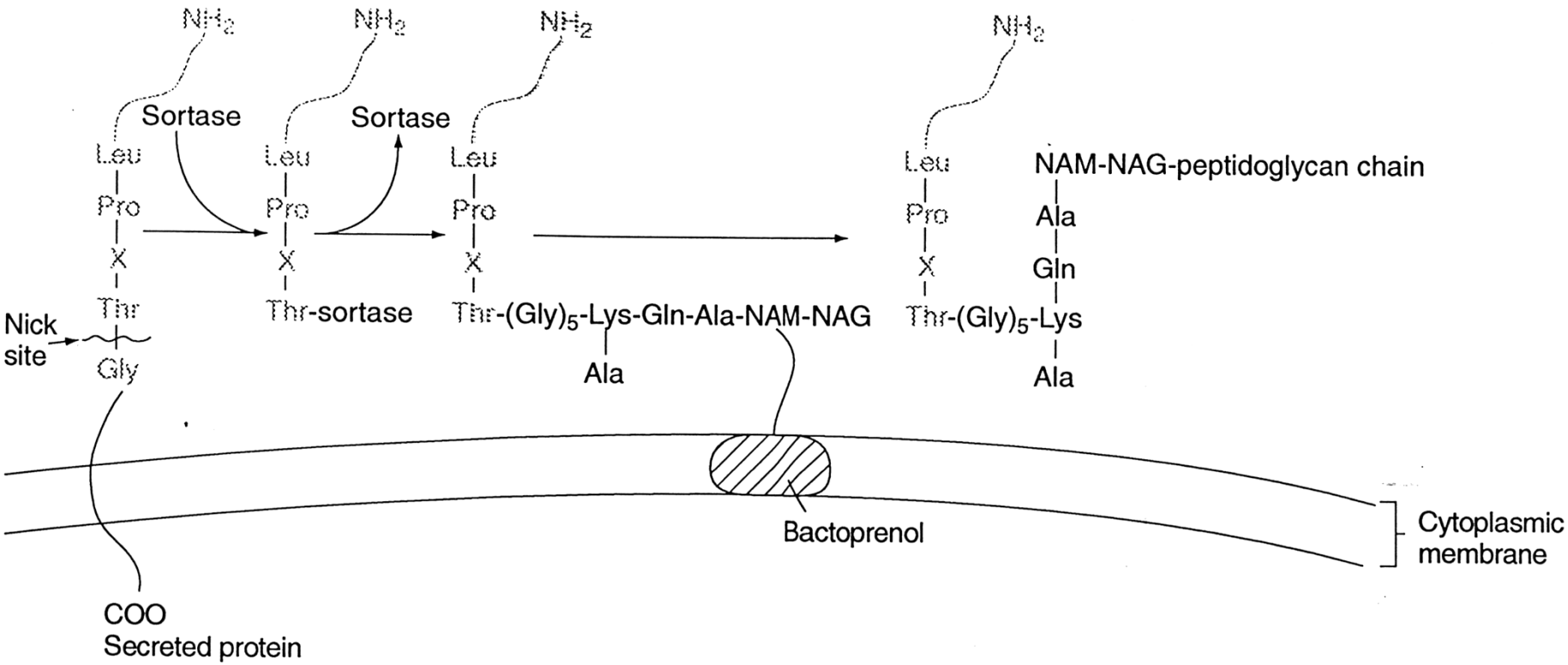
Methicillin resistant *S.* aureus (MRSA) are detected by their ability to grown on an agar medium containing 6ug/ml of oxacillin. Growth in 24hr incubation from a spot inoculum of MRSA is shown at the top and the lack of significant growth of a methicillin-susceptible *S. aureus* is shown at the bottom

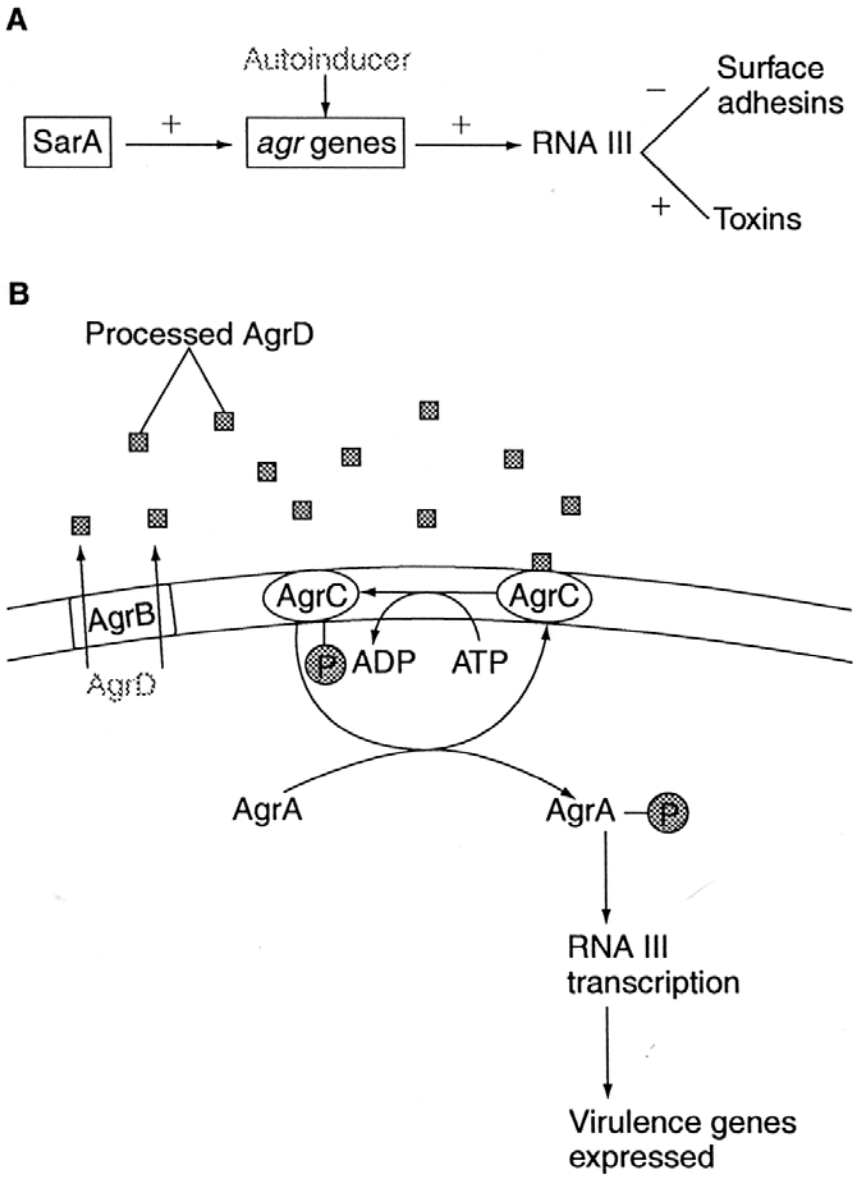
# Cell Wall Structure and Function

| Structure | Function |
|---|---|
| Capsule | Inhibits opsonization and phagocytosis<br>Protects from C′-mediated leukocyte destruction |
| Peptidoglycan | Osmotic stability<br>Stimulates production of endogenous pyrogen<br>Leukocyte chemoattractant<br>Inhibits phagocytosis and chemotaxis |
| Protein A | Binds IgG1, IgG2, IgG4 Fc receptors<br>Inhibits opsonization and phagocytosis<br>Leukocyte chemoattractant<br>Anticomplementary |
| Teichoic acid | Regulates cationic concentration at cell membrane<br>Receptor for bacteriophages<br>Attachment site for mucosal surface receptors |
| Cytoplasmic membrane | Osmotic barrier<br>Regulates transport into and out of cell<br>Site of biosynthetic and respiratory enzymes |

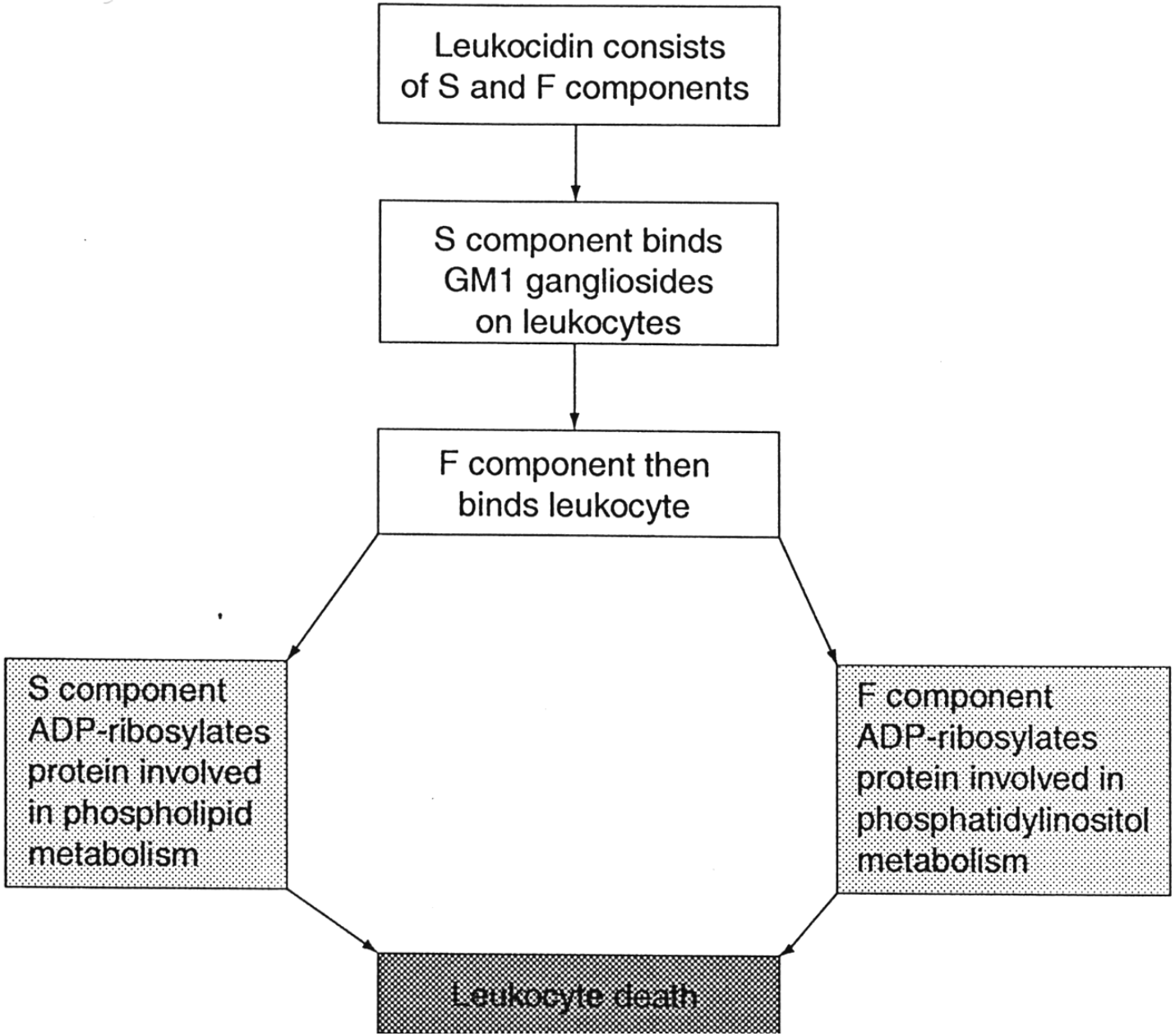



*S. Aureus* Surface Virulence Factors


NH2
NH2
NH2
NH2
Sortase
Sortase
Leu
Pro
X
Thr
Gly
Leu
Pro
X
Thr-sortase
Leu
Pro
X
Thr-(Gly)5-Lys-Gln-Ala-NAM-NAG
Ala
Leu
Pro
X
Thr-(Gly)5-Lys
Ala
NAM-NAG-peptidoglycan chain
Ala
Gln
Nick site
COO
Secreted protein
Bactoprenol
Cytoplasmic membrane

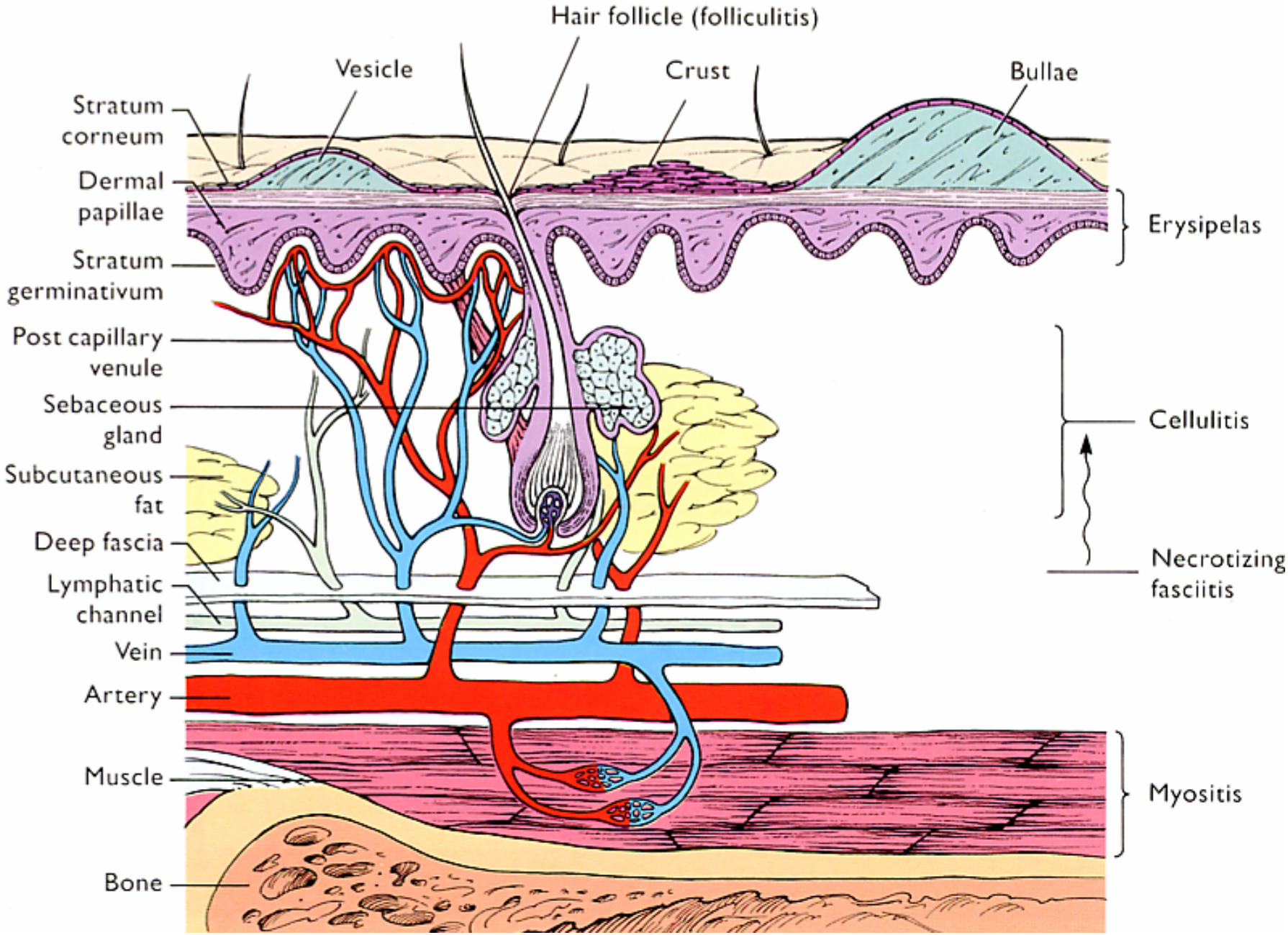


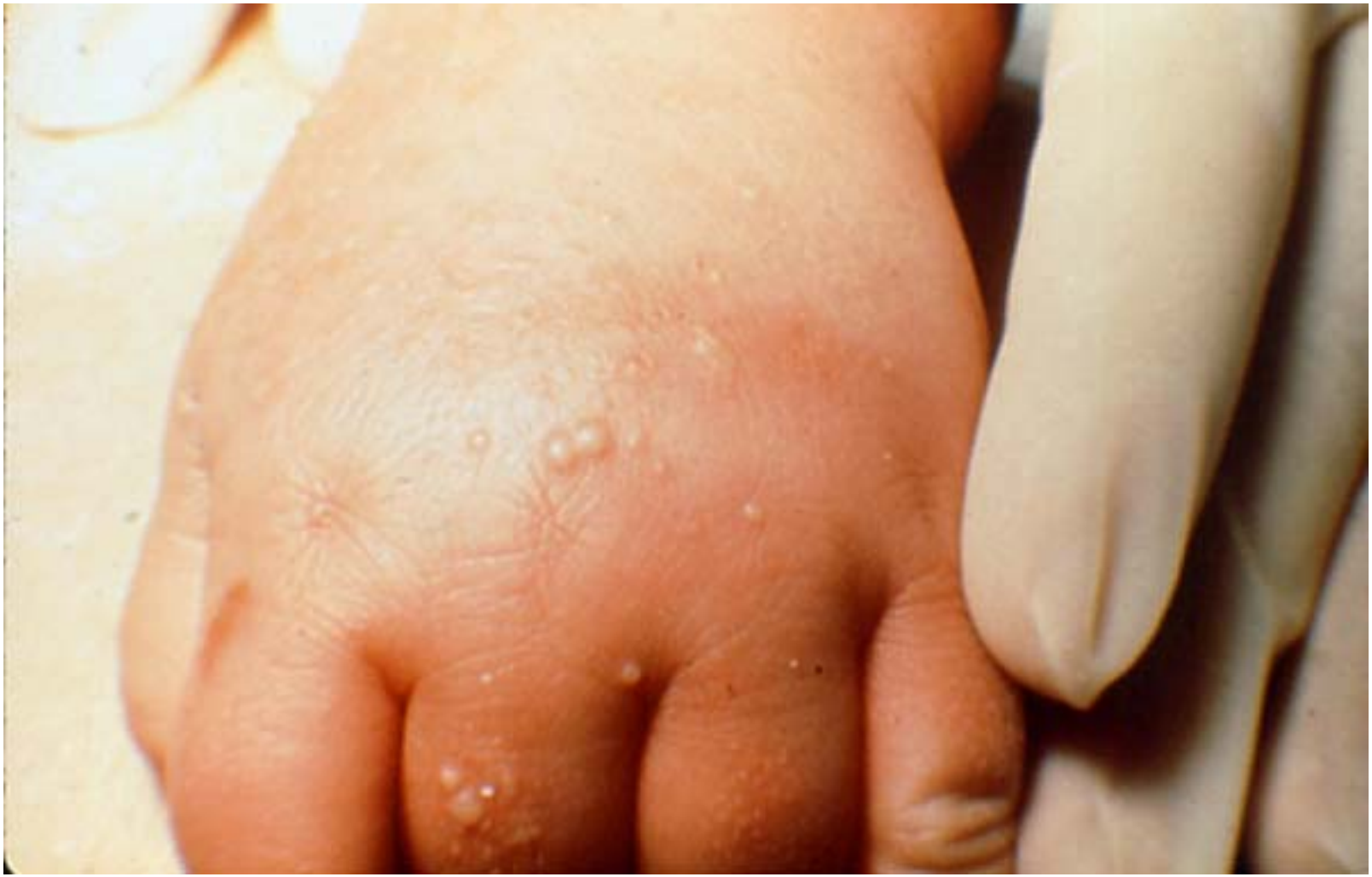

The AGR Pathway of Virulence Regulation in *S. aureus*


Leukocidin consists of S and F components
S component binds GM1 gangliosides on leukocytes
F component then binds leukocyte
S component ADP-ribosylates protein involved in phospholipid metabolism
F component ADP-ribosylates protein involved in phosphatidylinositol metabolism
Leukocyte death

# Clinical Manifestations

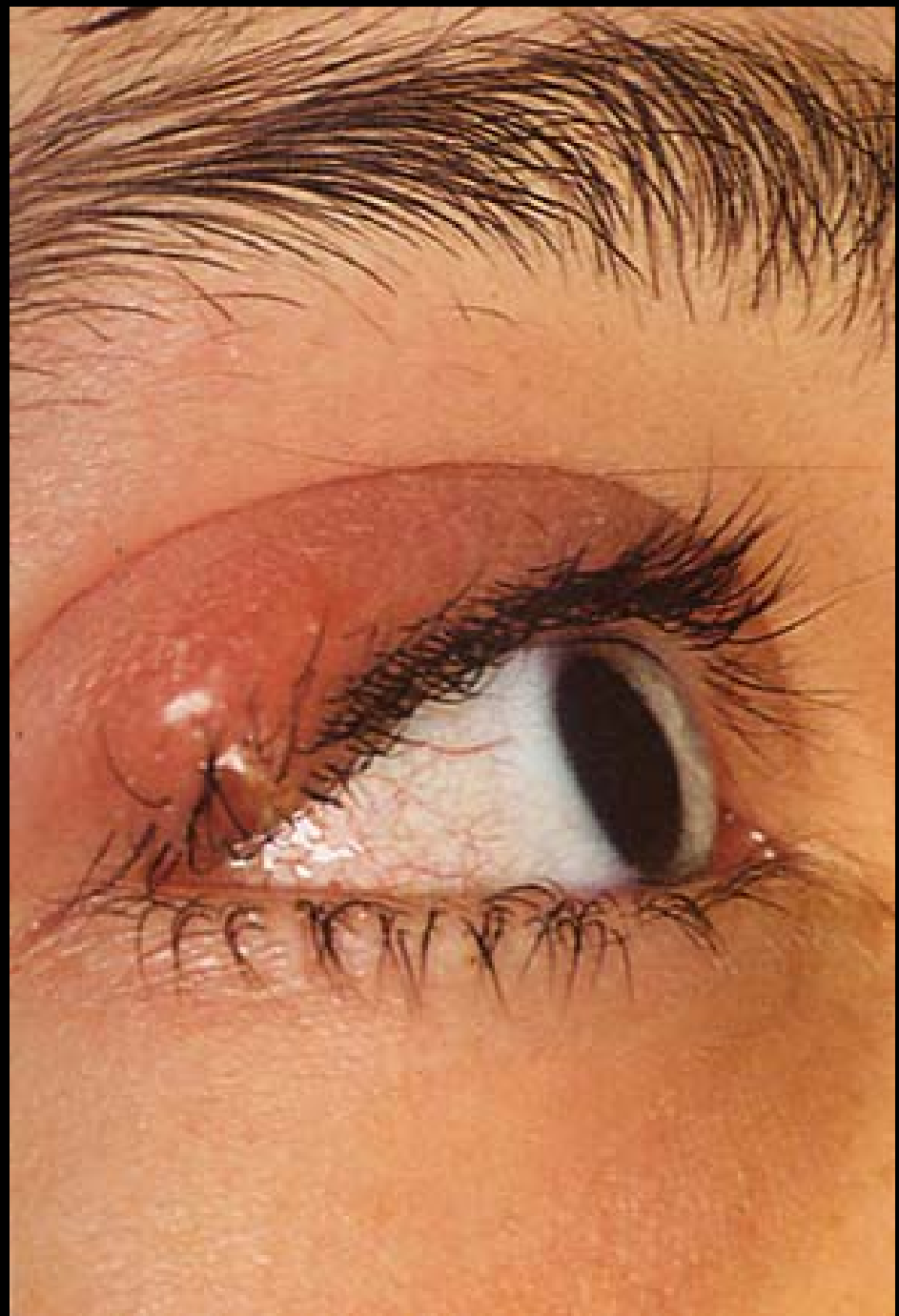
The basic anatomic lesion is the abscess. Toxins produced by the organism may predominate the clinical picture. Even the most benign localized infection can occasionally become the seeding site for a devastating systemic disease.

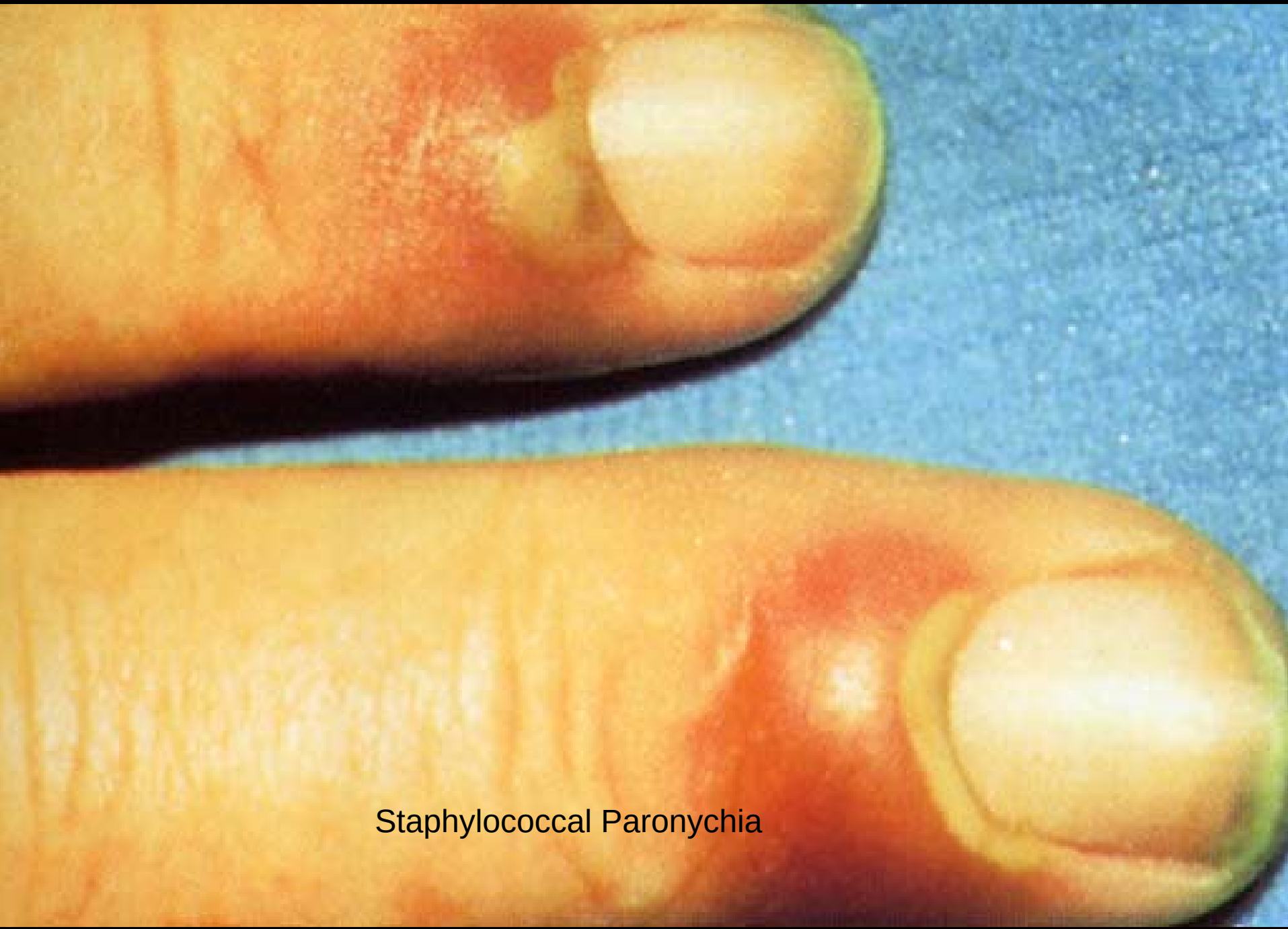

Hair follicle (folliculitis)
Vesicle
Crust
Bullae
Stratum corneum
Dermal papillae
Stratum germinativum
Post capillary venule
Sebaceous gland
Subcutaneous fat
Deep fascia
Lymphatic channel
Vein
Artery
Muscle
Bone
Erysipelas
Cellulitis
Necrotizing fasciitis
Myositis



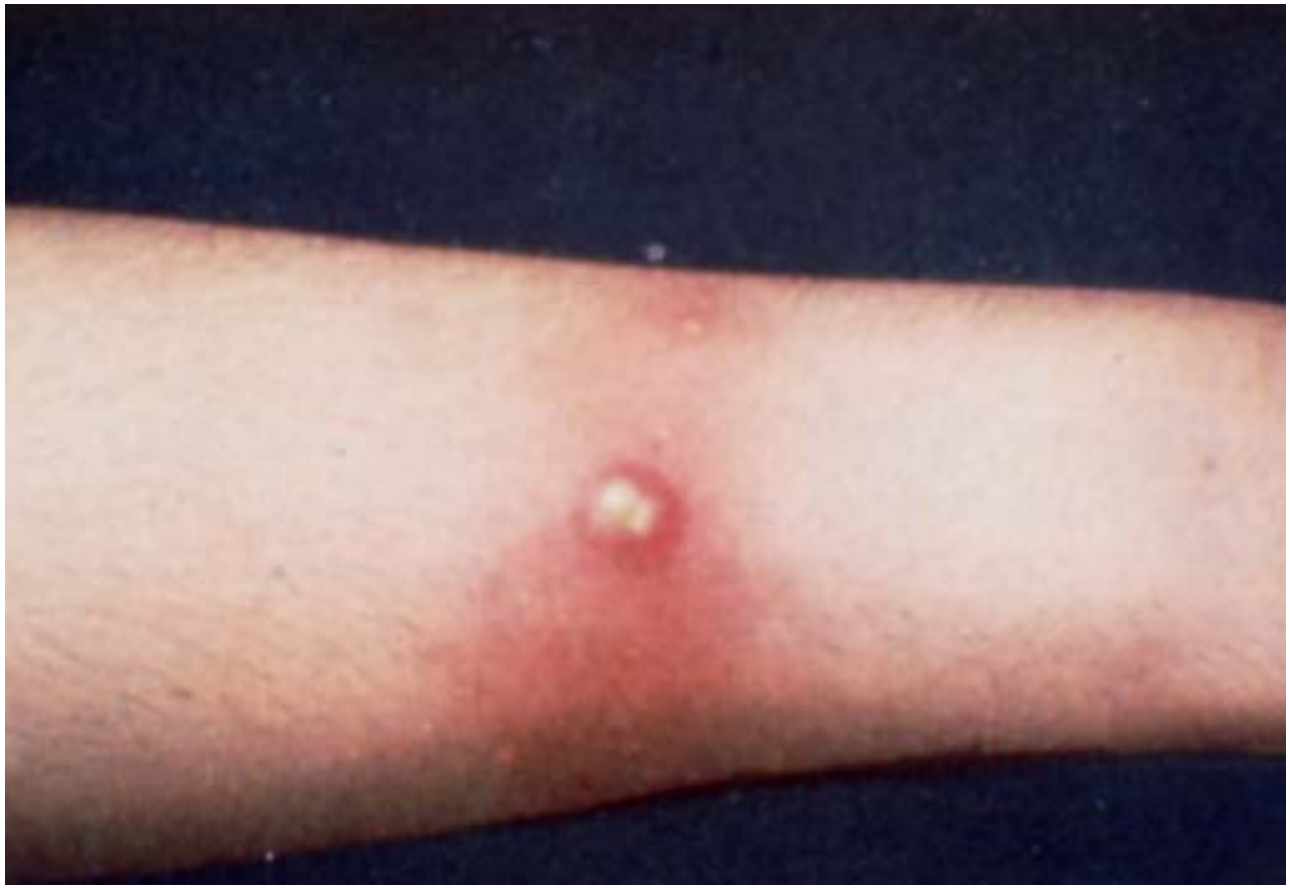
**Staphylococcal folliculitis**

Staphylococcal Stye

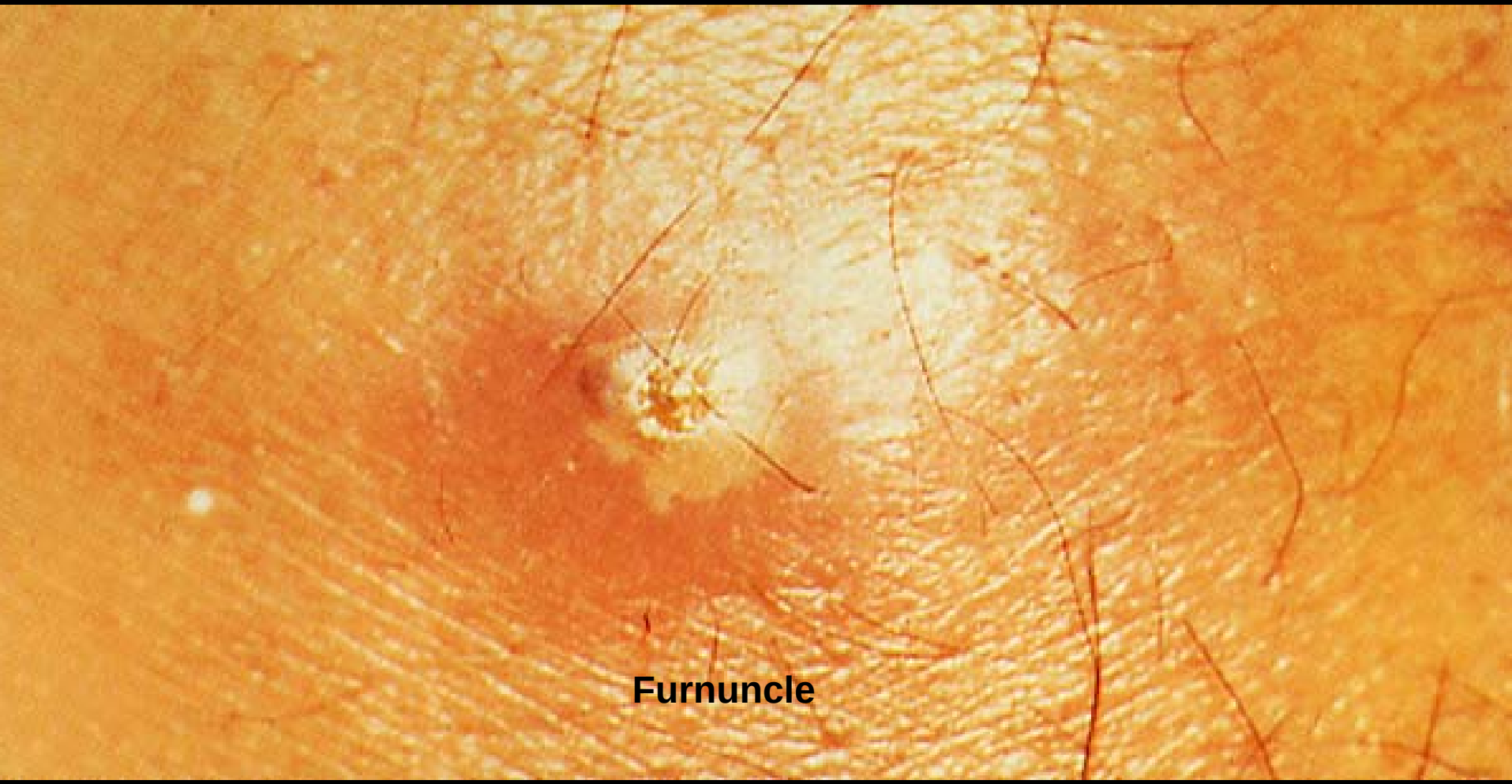




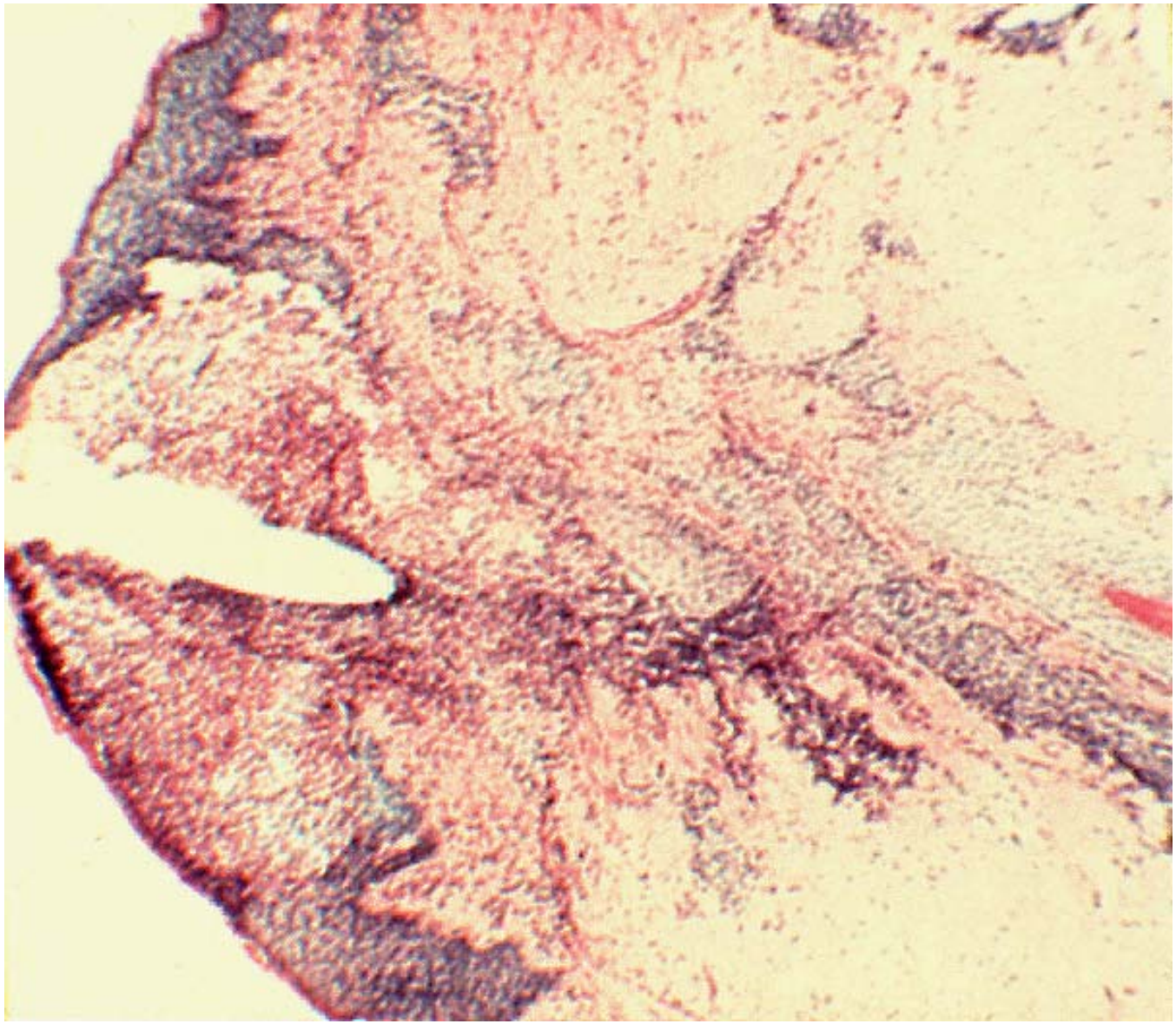
Staphylococcal Paronychia



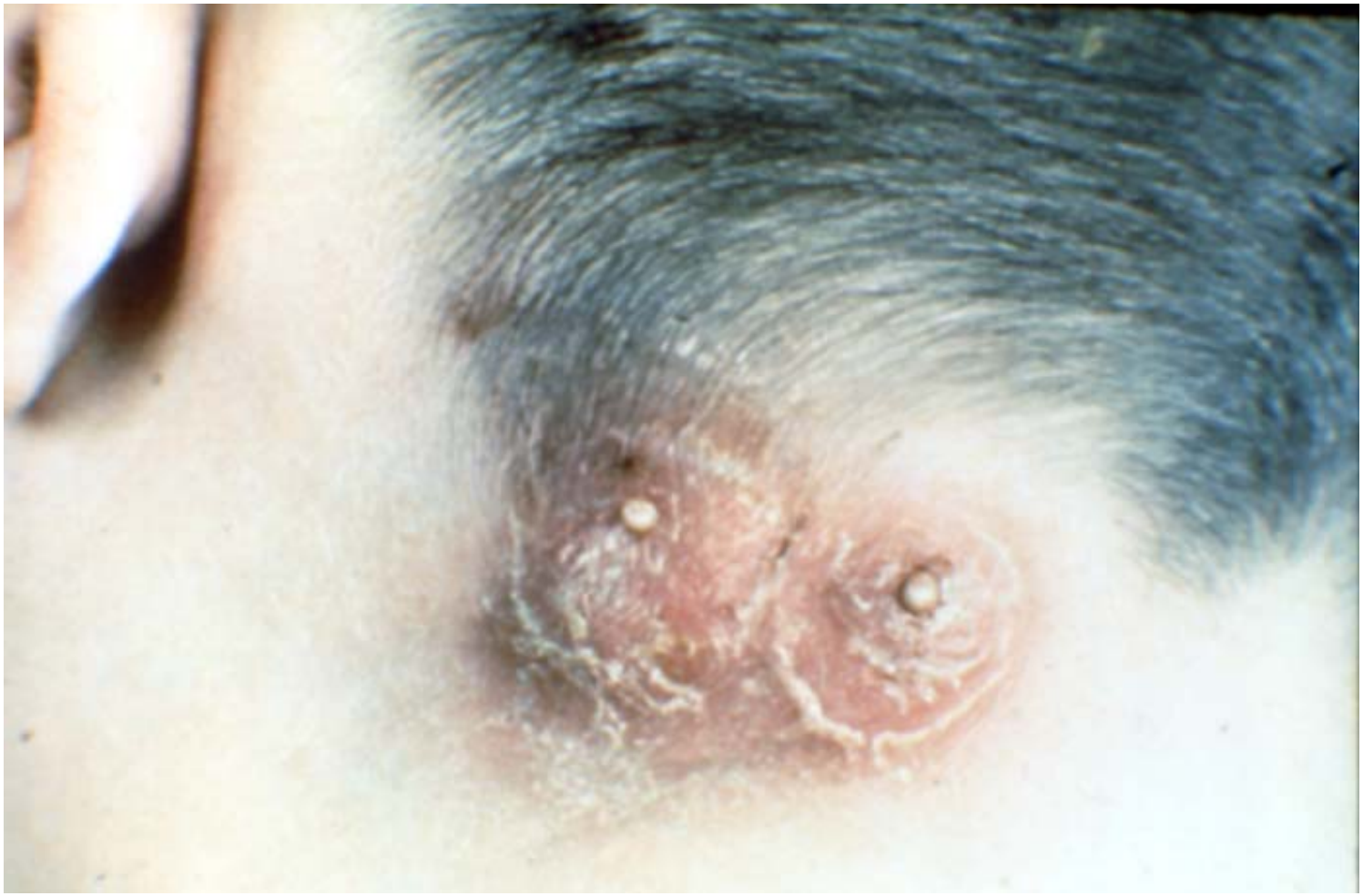
**Staphylococcal furuncle better known commonly as a “ Boil”**



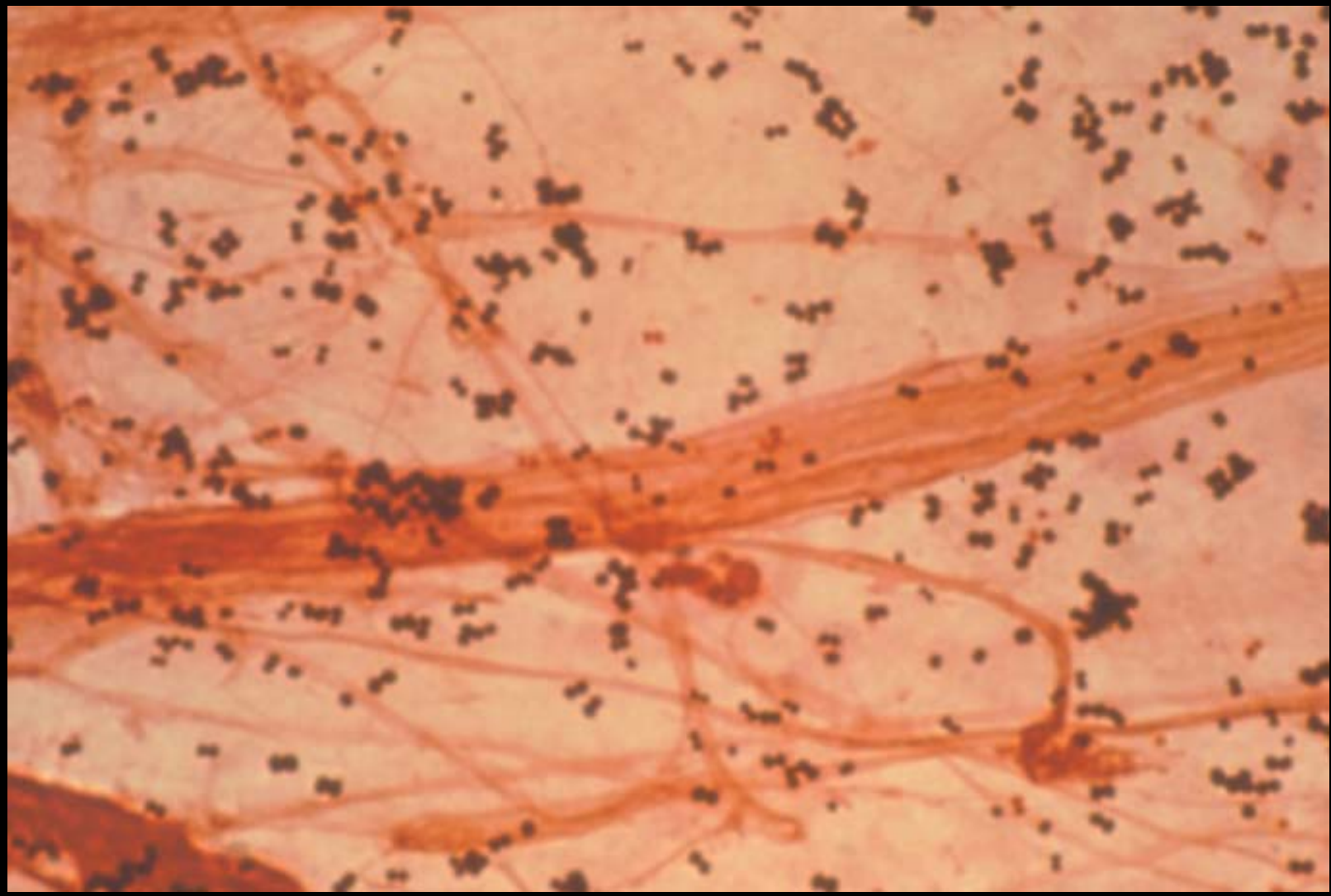
Furnuncle



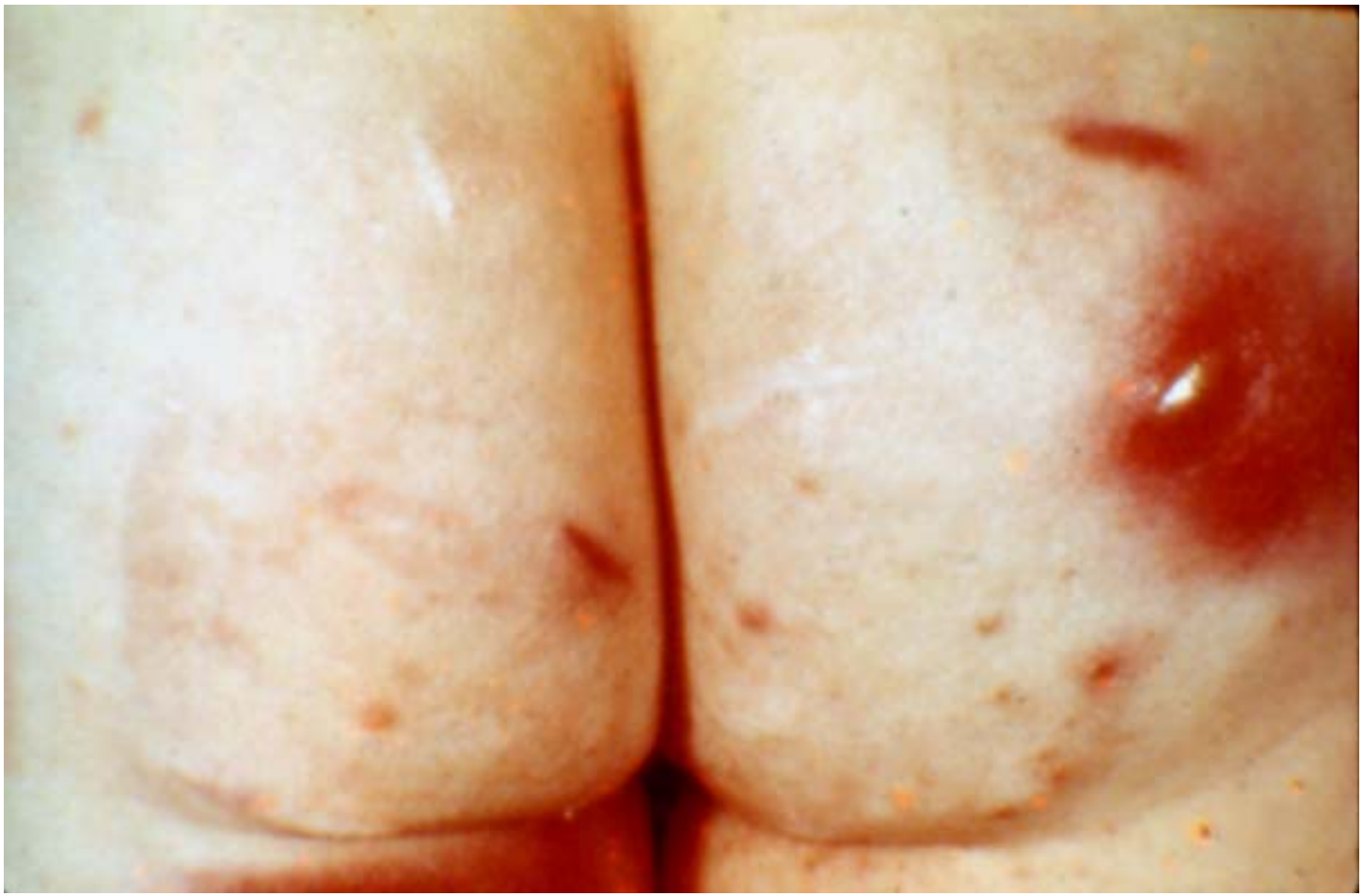
Resolving Staphylococcal abscess after drainage



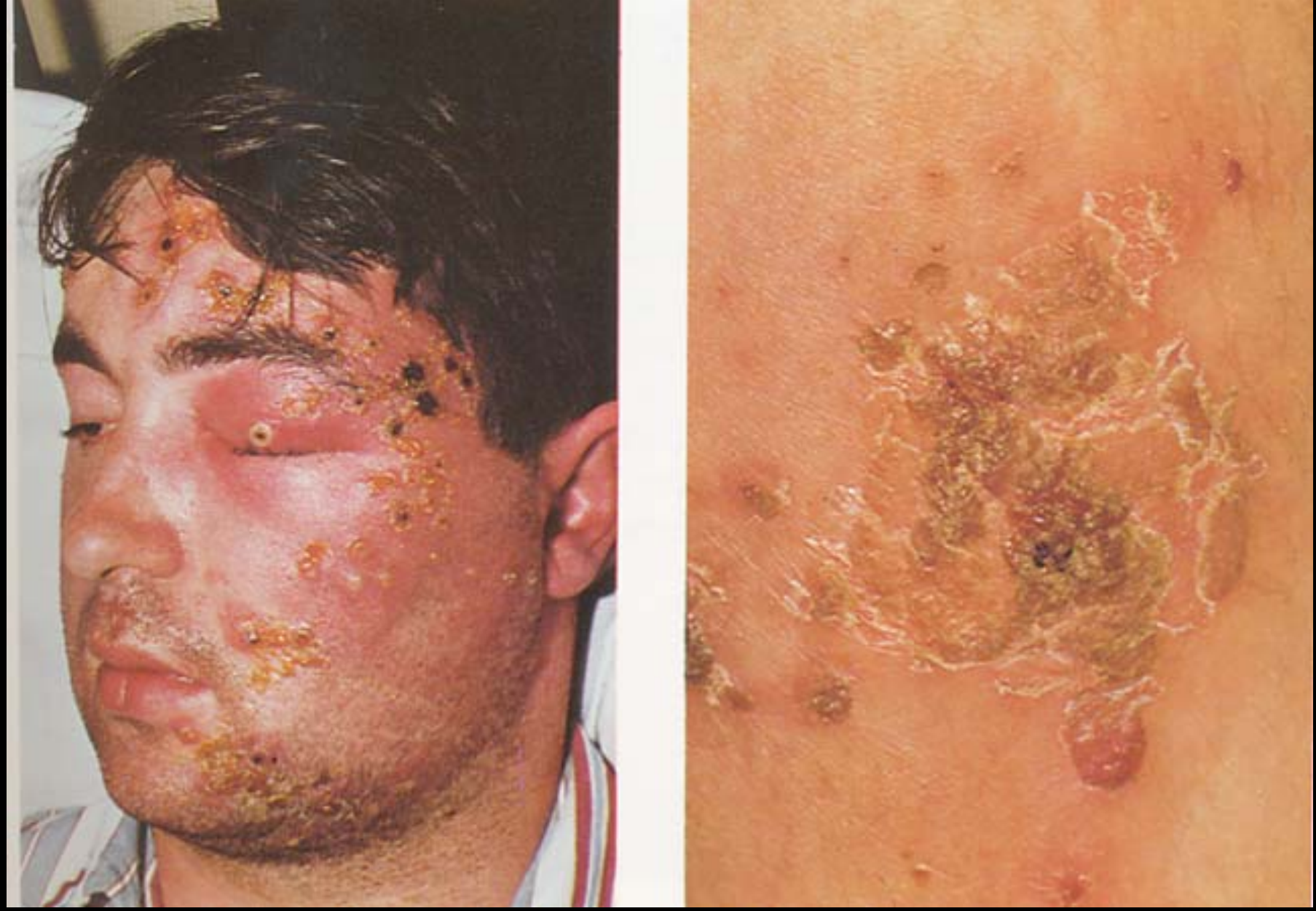
**Staphylococcal carbuncle**



Staphylococci in Lung Infection

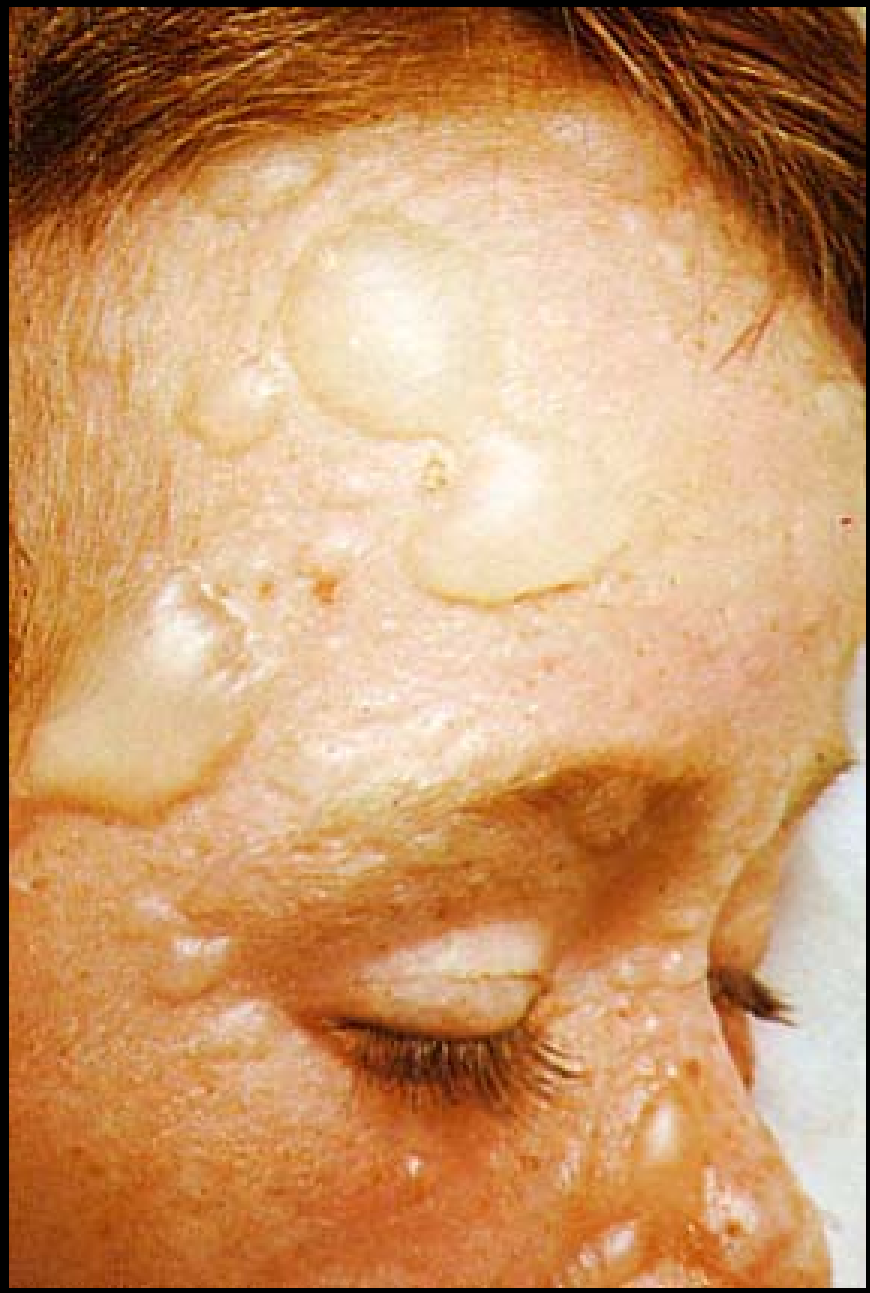


**There is no end to the trouble that staphylococcal infection can cause**



Staph.aureus Pustular Impetigo

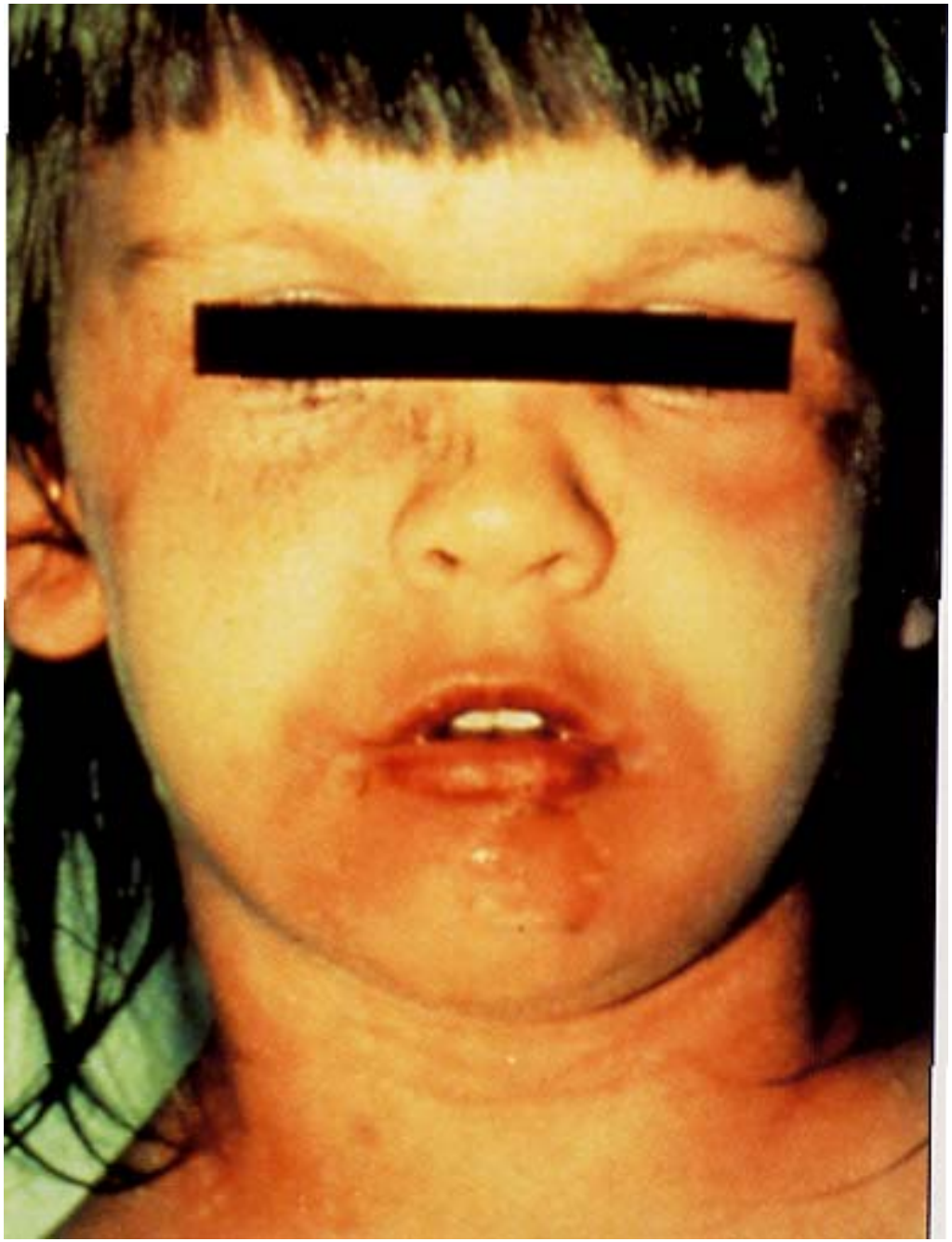
Staph. aureus
Bullous Impetigo

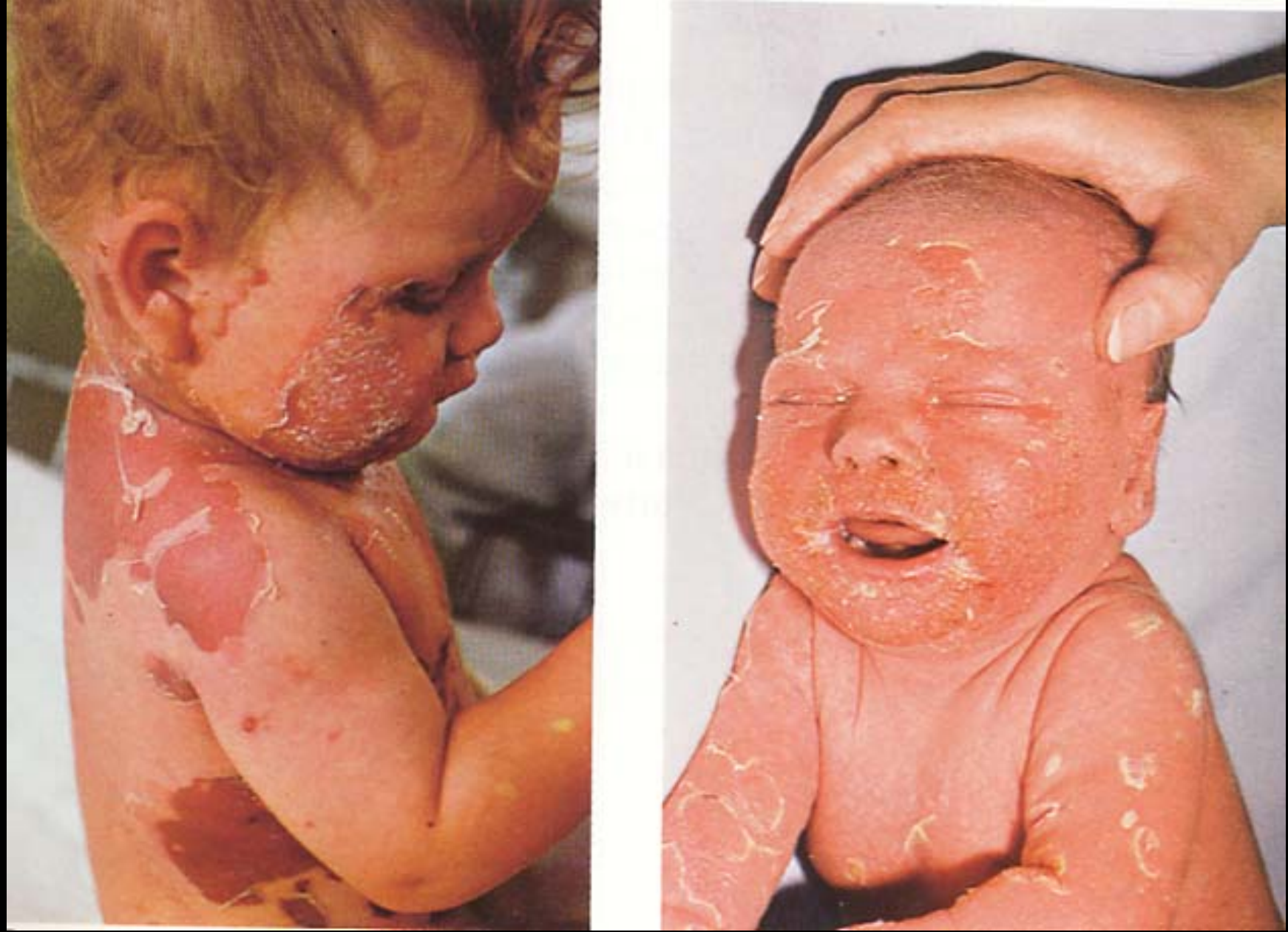


Staphylococcal Scalded Skin Syndrome. Erythema is prominent on the neck and around the eyes and mouth. Crusting is also apparent.

The usual sequence of this disease is:

1. Cutaneous erythema
2. Development of superficial vesicles and bullae.
3. Skin separation in sheets and ribbons leaving a moist red base that dries quickly.

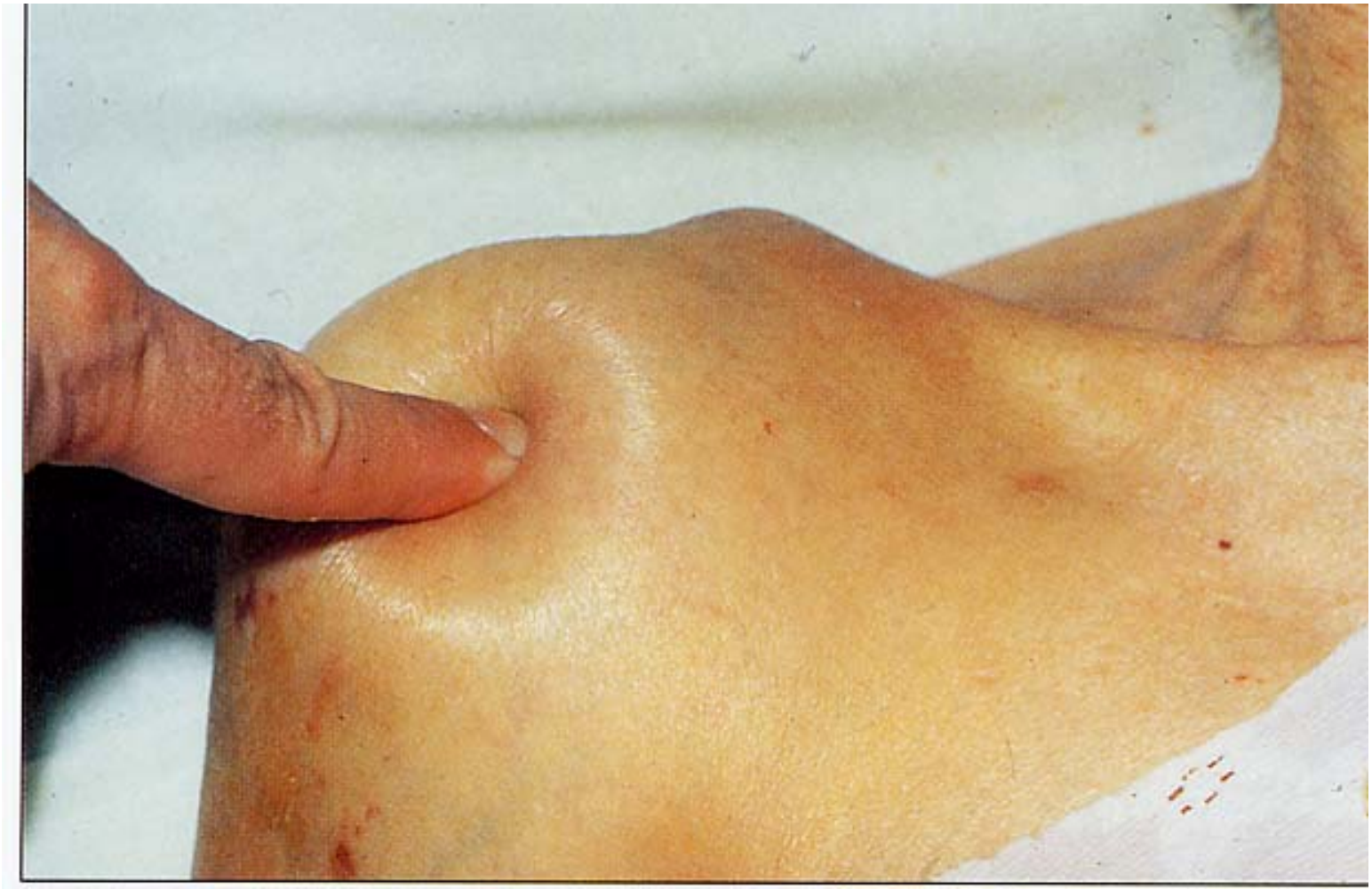




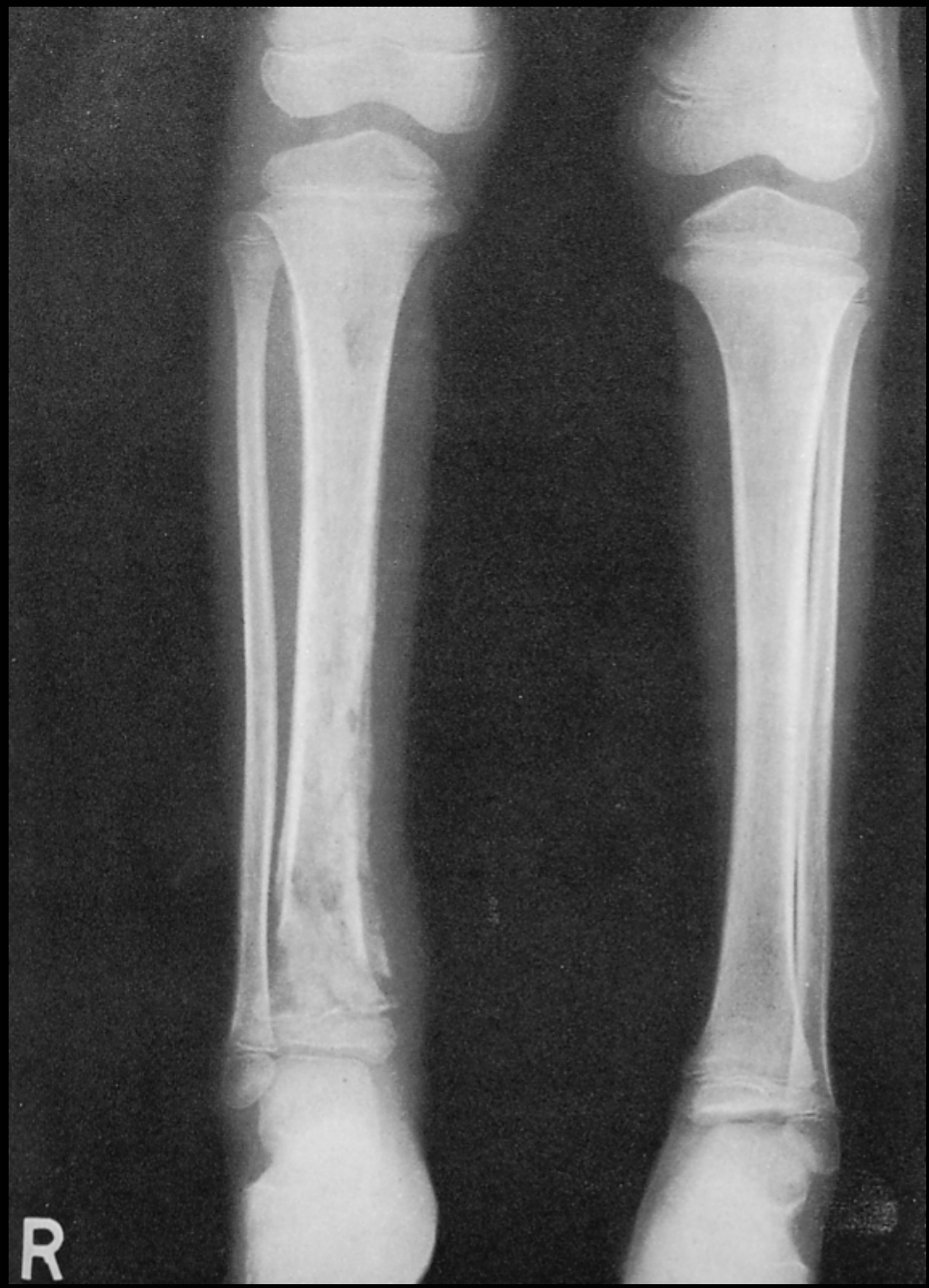
Scalded skin Syndrome

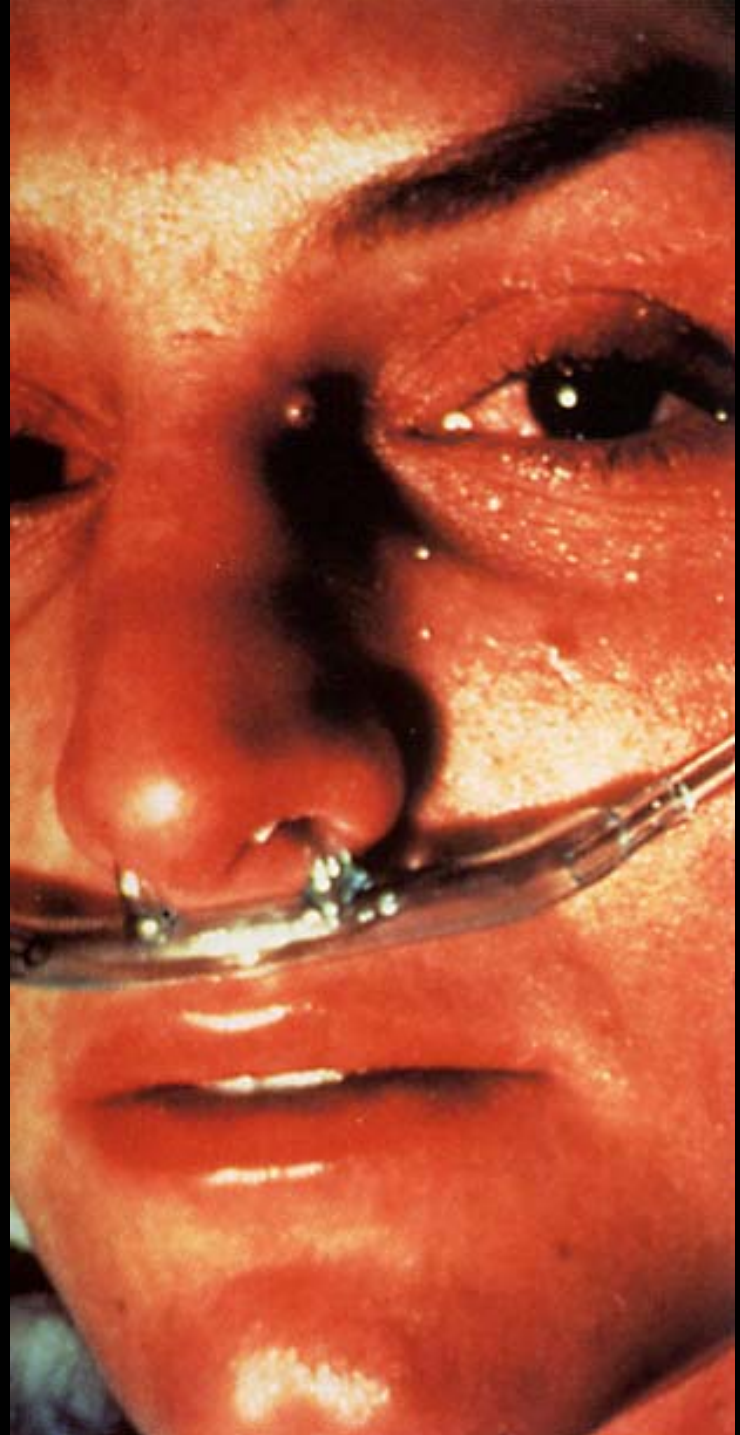
## TABLE 22-4 Characteristics of Exfoliative Toxins

| PROPERITES | EXFOLIATIVE TOXIN A | EXFOLIATIVE TOXIN B |
|---|---|---|
| Size | 24,000 daltons | 24,000 daltons |
| Temperature tolerance | Stable (100° C, 20 min) | Labile (60° C, 30 min) |
| EDTA treatment | Inactivated | No effect |
| DNA | Chromosomal | Plasmid |



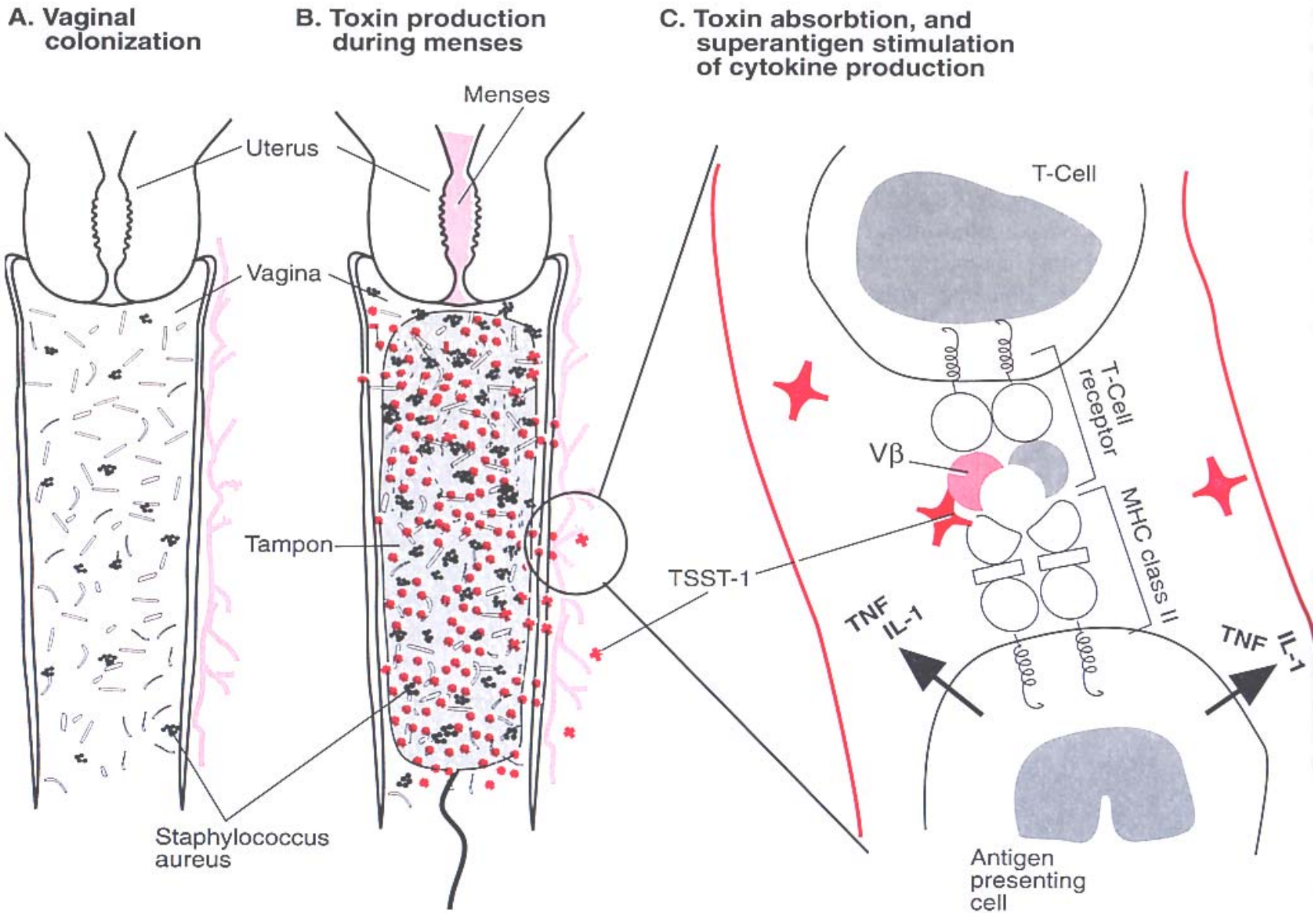
Septic arthritis. Following elective surgery complicated by a staphylococcal wound infection, this woman was re-admitted with fever, right shoulder pain and lumbar backpain. Needle aspiration of the right shoulder and an intravertebral disk revealed a coagulase positive *Staphylococcus aureus.*

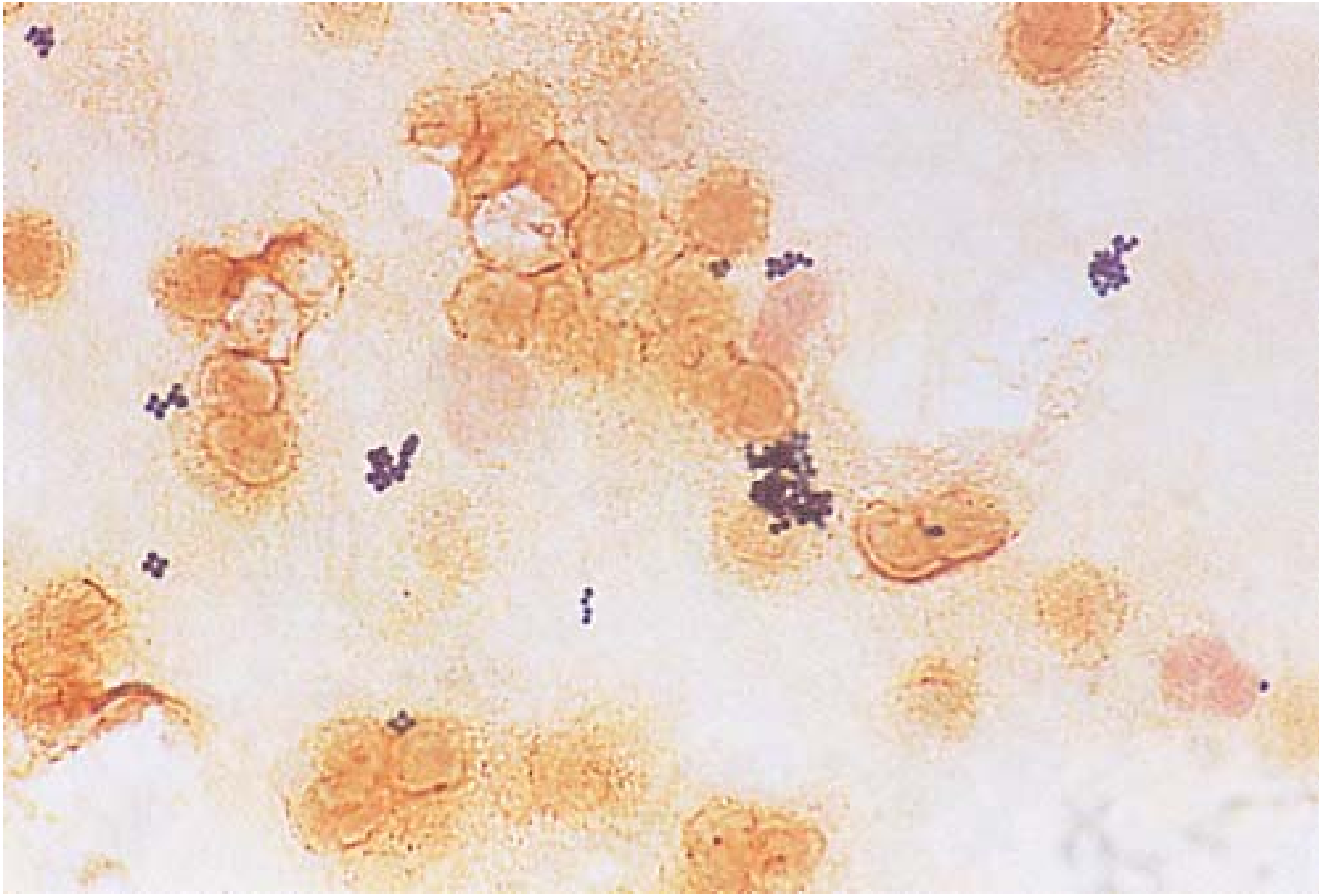

R



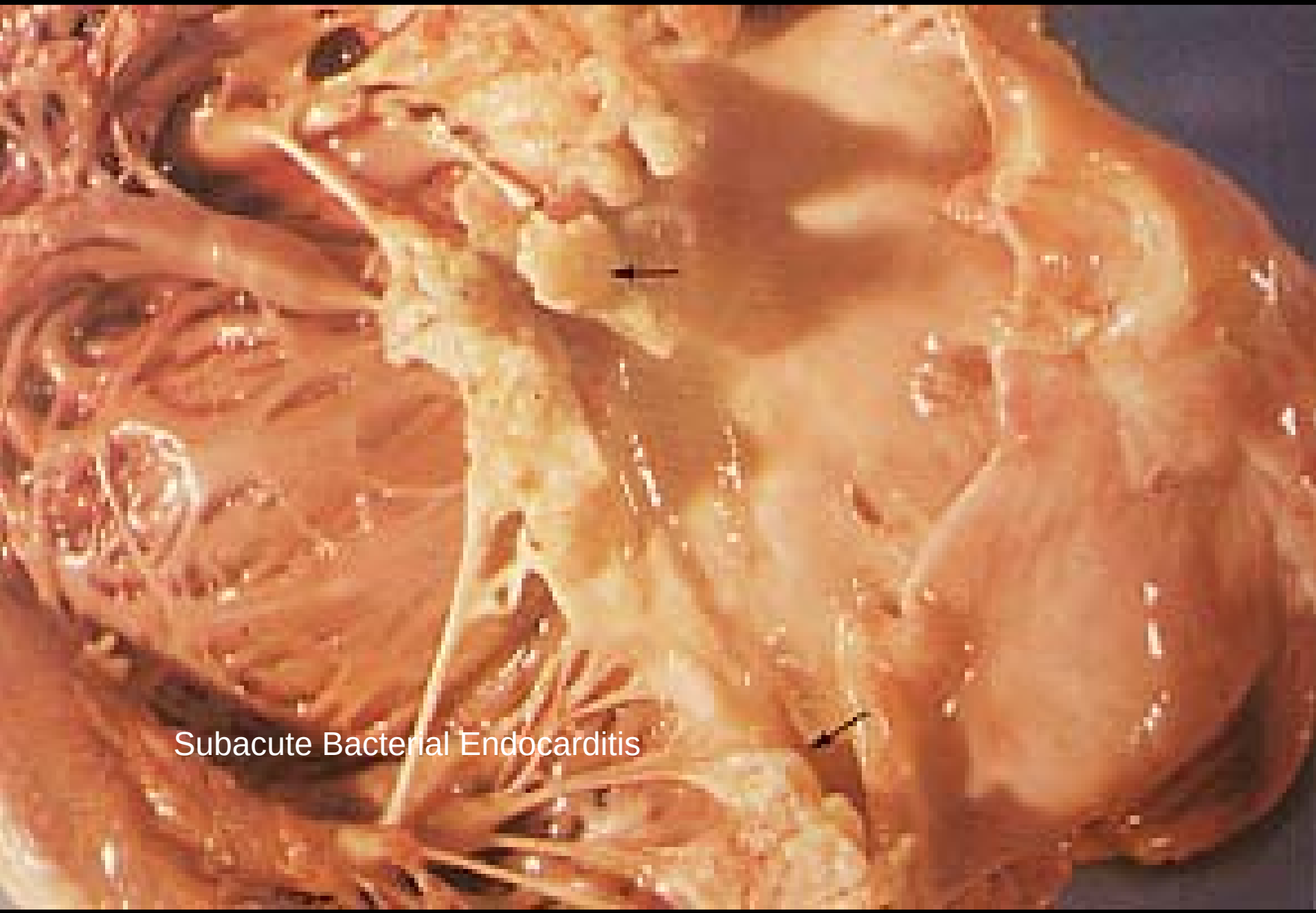
Staphylococcal Toxic Shock Syndrome

# The Natural History of Staphylococcal Toxic Shock Syndrome





Gram stain of *Staphylococcus aureus* from a positive blood culture bottle showing typical gram positive cocci in pairs , tetrads and grape-like clusters.


Subacute Bacterial Endocarditis

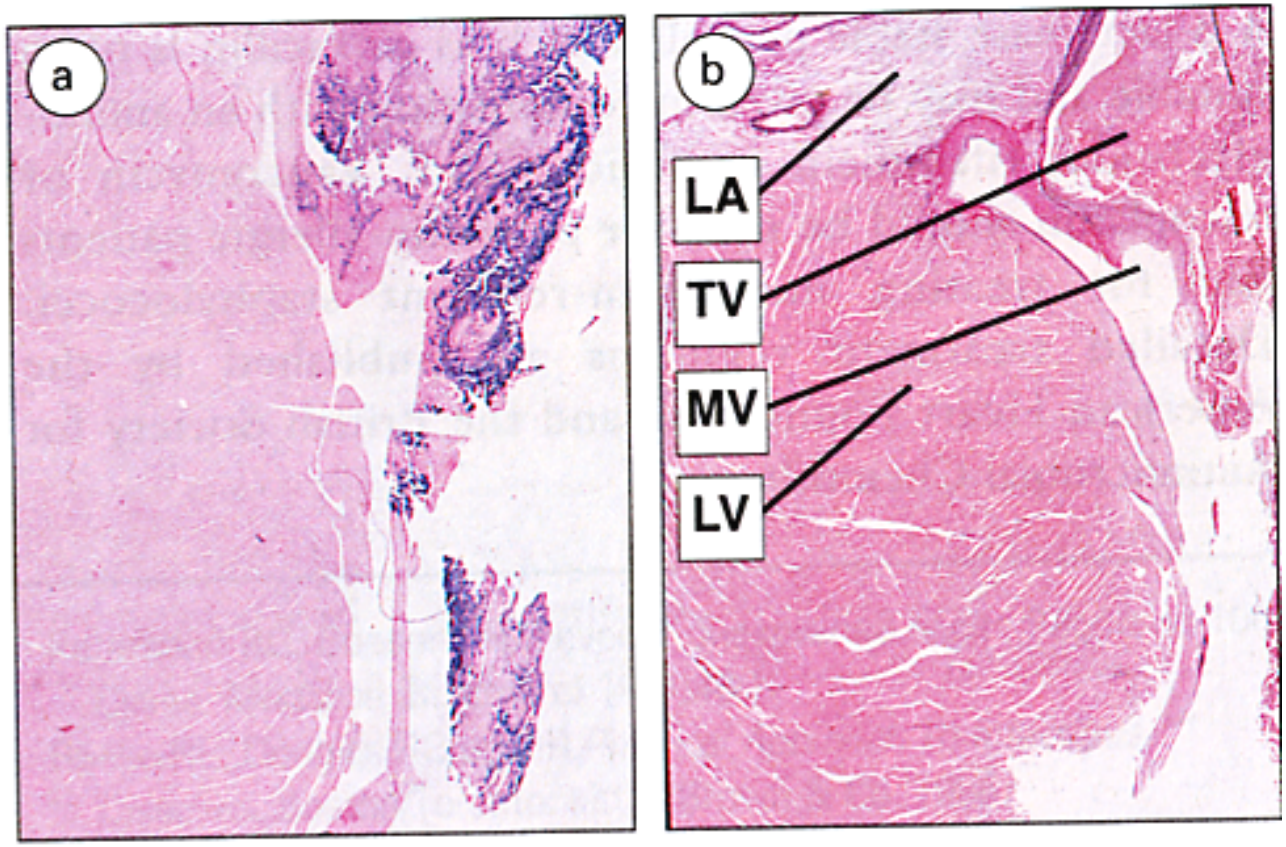
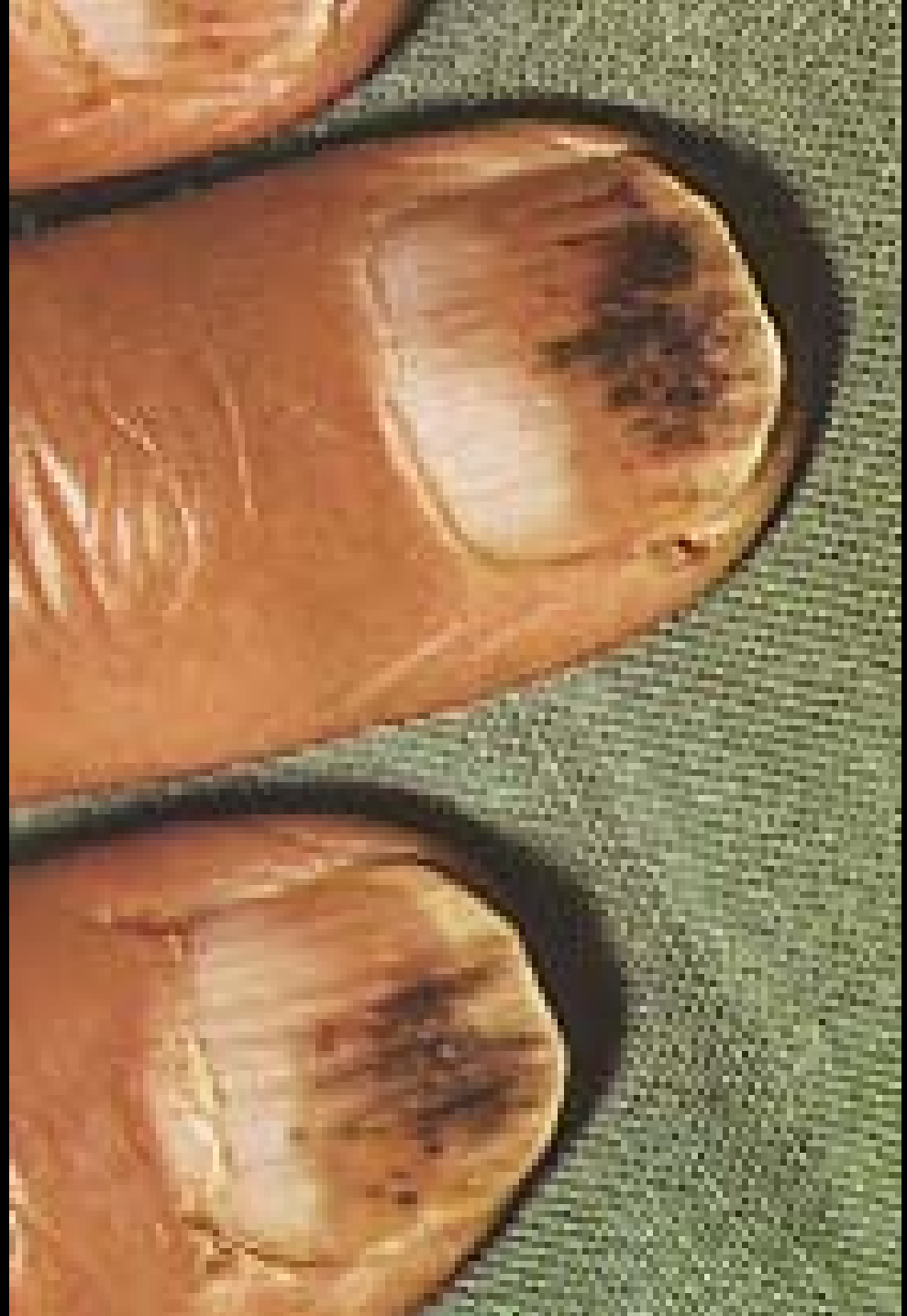
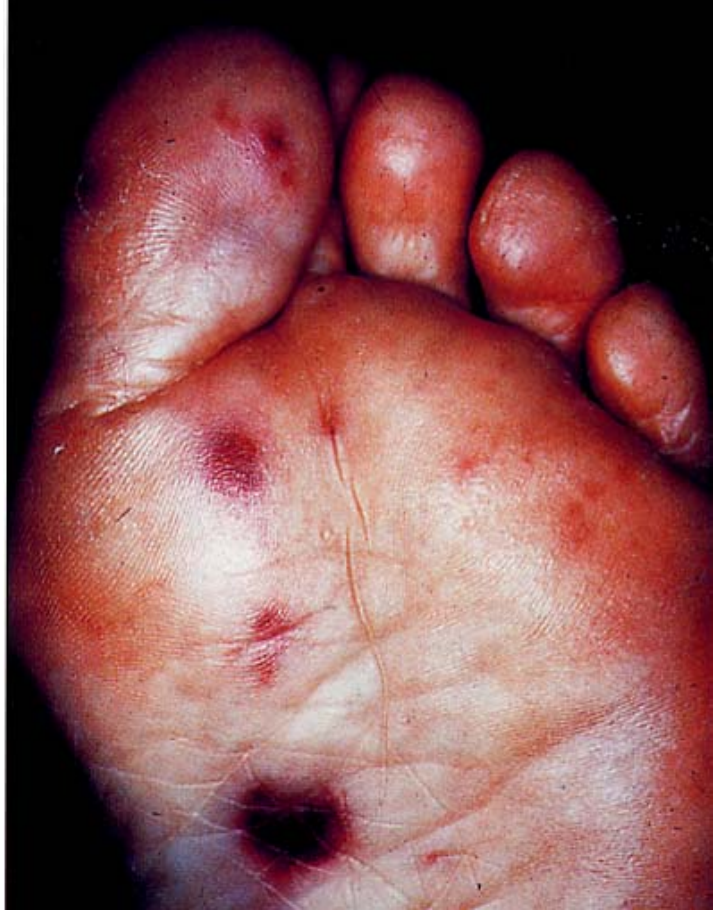
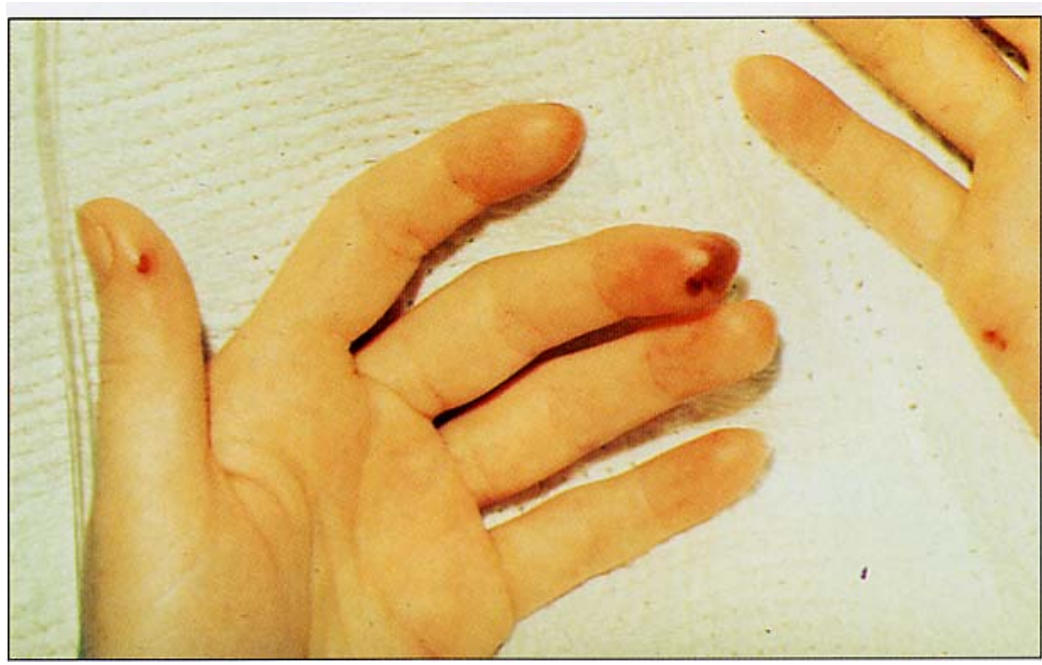



**Fig. 27.10** Bacteria circulating in the bloodstream adhere to, and establish themselves on, the heart valves. Multiplication of the microbes is associated with destruction of valve tissue and the formation of vegetations, which interfere with, and may severely compromise, the normal function of the valve. These histologic sections show the virtual destruction of the leaflet at the mitral valve by staphylococci. (a) Gram stain. (b) Eosin-Van Geisen stain. (LA, left atrium; LV, left ventricle; MV, remnant of mitral valve; TV, thrombotic vegetation.) (Courtesy of RH Anderson.)



*Staph. Sureus*
Sepsis
Splinter Hemorrhages

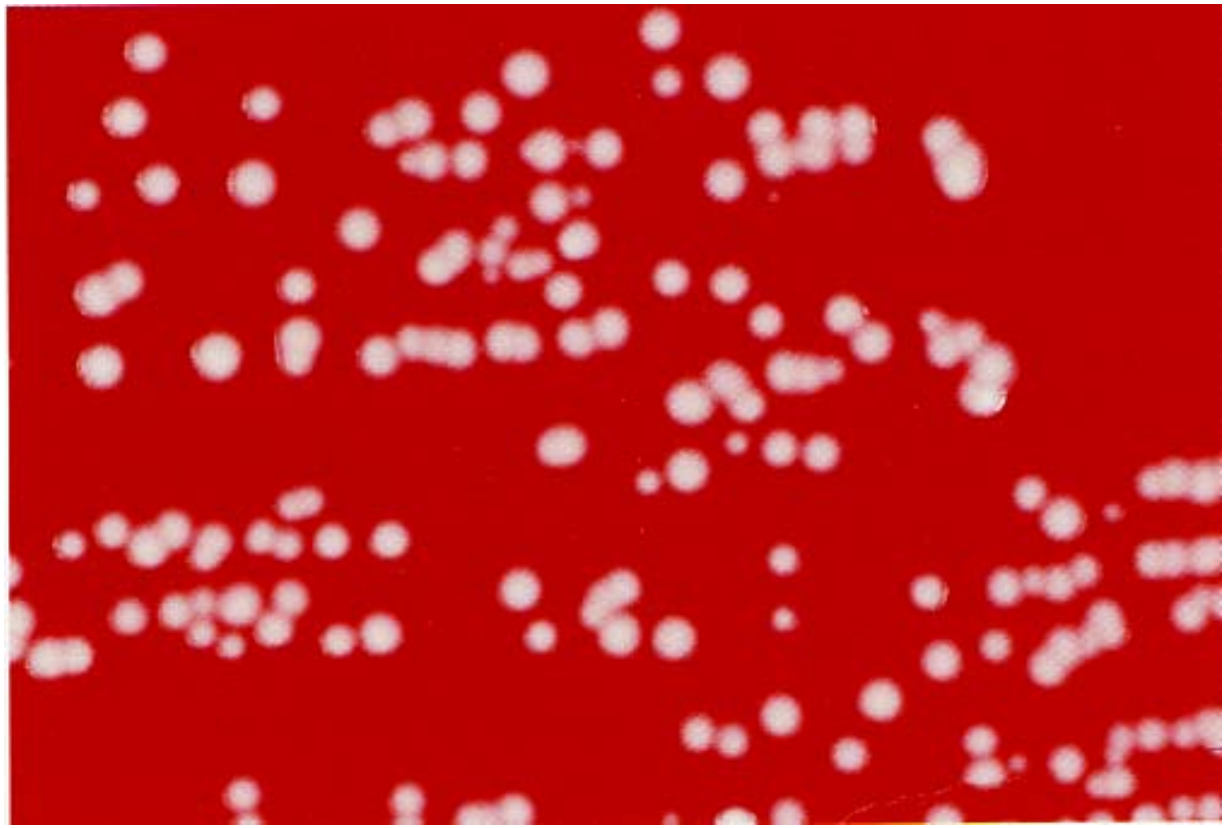




The left-hand figure shows Janeway lesions in a patient with *S. aureus* endocarditis. Janeway lesions are generally painless, flat and, as shown here occasionally hemorrhagic. Embolic in origin with microabscesses in the dermis they are considered to be pathognomic of *S. aureus* endocarditis. On the right is another example from a case of *S. aureus* endocarditis secondary to intravenous drug use. This patient also has Osler's nodes, painful lesions in the tufts of the fingers and toes. Osler's nodes are likely an immunologic phenomenon. These lesions have become relatively uncommon in the anti-microbial era but if there is a significant delay in therapy they can be seen.

**INFECTIONS INVOLVING *STAPHYLOCOCCUS EPIDERMIDIS***

| infection of: | % of infections caused by *Staph. epidermidis* |
|---|---|
| prosthetic heart valve | |
| early (<2 months postoperatively) | 30–70 |
| late (>2 months postoperatively) | 20–30 |
| Prosthetic hip | 10–40 |
| Cerebrospinal fluid shunt | 30–65 |
| Vascular grafts | 5–20 |
| Peritoneal dialysis related | 30 |
| Intravascular catheters | 10–50 |



Growth of *Staphylococcus saprophyticus* on 5% sheep blood agar
These coagulase negative stapylococci are often found as the cause of first-time urinary tract infection in sexually-active women.

*S. saprophyticus* can be distinguished from other species of coagulase negative staphylococci by their resistance to novobiocin (right). The novobiocin susceptible staphylococcus is on the left.