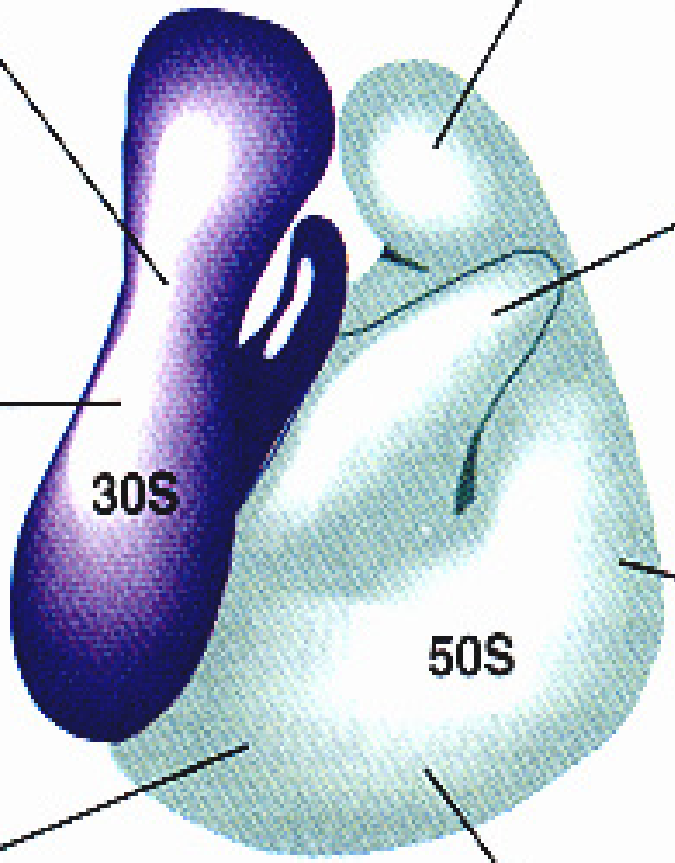
Chemotherapy, what do shamans have to do with it?

Modes of Synthetic Agents:

- Sulfonamides = sulfa drugs (bacteriostatic)
  - Mechanism of action: similar structure to p-amino benzoic acid = competitive inhibitor of folic acid metabolism
  - Clinical applications: mix with trimethoprim =Bactrim or Septra; used to treat UTIs
- Other synthetic agents:
  - Sulfones (Dapsone): used in leprosy
  - p-Aminosalicylic acid (PAS): used in tuberculosis
  - Isoniazid (INH): inhibits mycobacterium cell wall
  - Ethambutol: also inhibits TB cell walls

Modes of Antibiotics:

- Inhibition of cell wall synthesis-
  - Penicillins, cephalosporins, vancomycin, penems
- Inhibit Protein synthesis-
  - 50s inhibitors: Erythromycin, clindamycin, chloramphenicol
  - 30s inhibitors: Tetracyclines, aminoglycosides
- Inhibit Nucleic acid Metabolism-
  - Quinolones, rifampin, sulfa drugs
- Alter Cell Membrane Permeability-
  - Nystatin, Amphotericin B, Polymyxin,



Aminoglycosides
Blocks the initiation of translation and causes the misreading of mRNA

Macrolides
Prevents the continuation of protein synthesis

Chloramphenicol
Prevents peptide bonds from being formed

Tetracyclines
Blocks the attachment of tRNA to the ribosome

Lincosamides
Prevents the continuation of protein synthesis

Streptogramins
Each interferes with a distinct step of protein synthesis

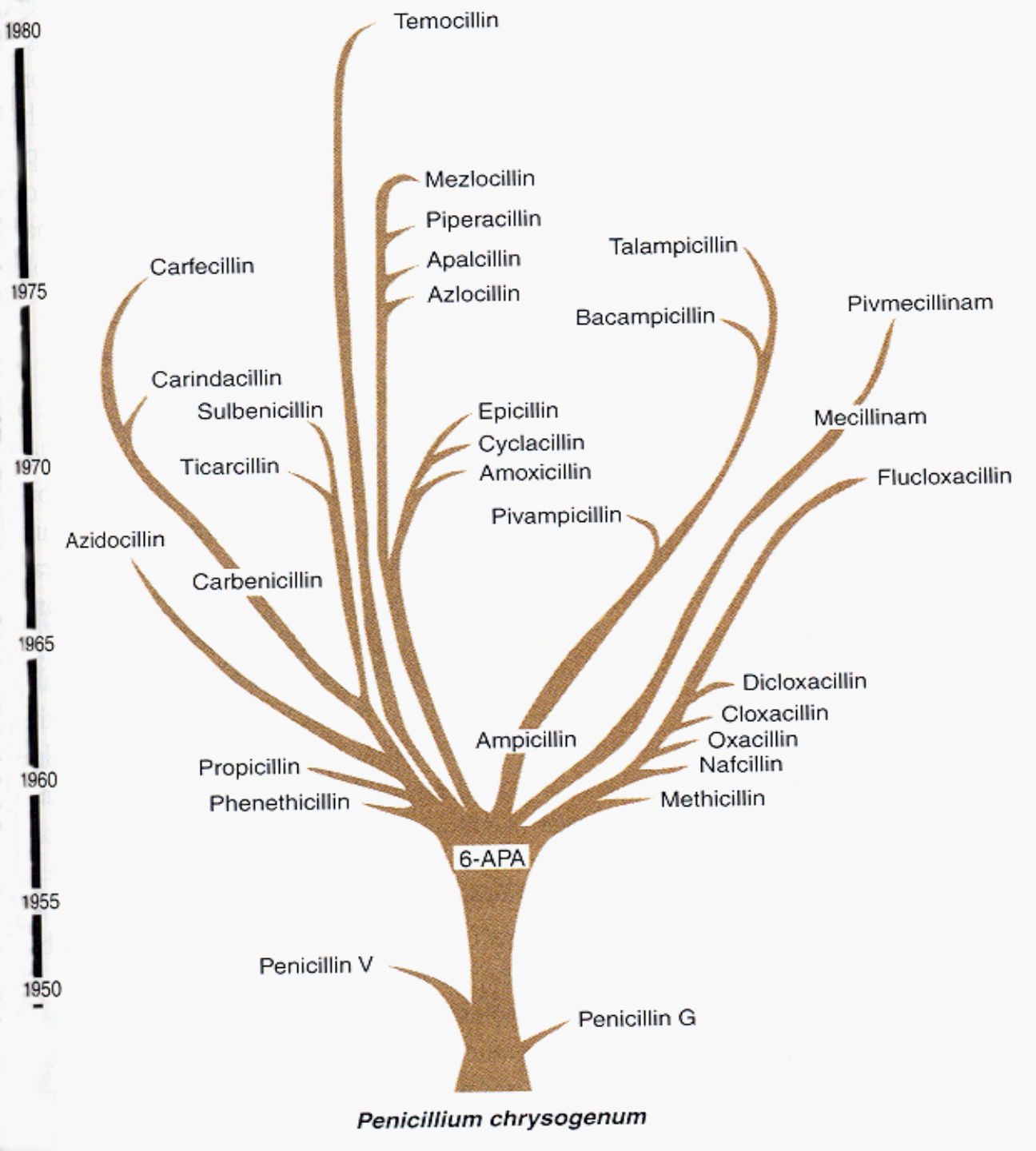
Oxazolidinones
Thought to interfere with the initiation of protein synthesis

Types of Antibiotics:

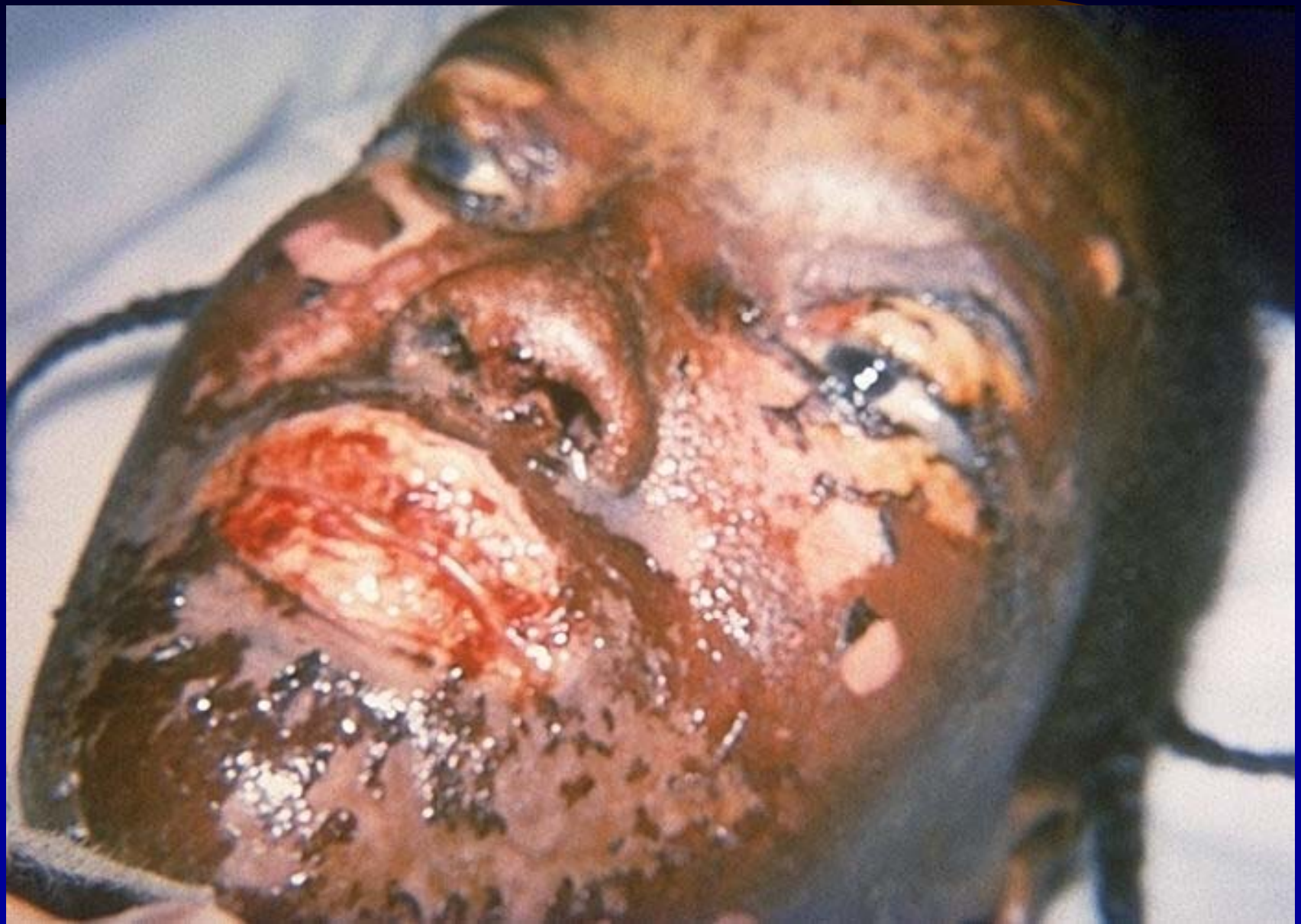
- Penicillins: (6 Aminopenicillanic acid)
  - B-lactam; inhibits cross-linking of peptidoglycan by preventing addition of acetylmuramic acid
  - Natural: Penicillin G, V, F, K, X
  - Biosynthetic: Penicillin V, O, (G)
  - Semisynthetic: Methicillin, Oxacillin, Ampicillin
- Cephalosporins: Broad spectrum
  - Like Penicillin, it is fungal-derived
  - Composed of 2 rings: *B*-lactam
  - Inhibit cross-linking of peptidoglycan
  - Expensive, especially compared to penicillin

6-APA is the basic parent compound which, when modified becomes the many forms of Penicillin in present use

- -longer shelf-life
- -acid resistance
- -broader spectrum



Severe penicillin allergy



Types of Antibiotics:

- Tetracyclines: Broadest spectrum
  - Bind 30s subunit; blocks incoming t-RNA binding
  - Affinity for fast-growing tissues; new bone and discoloring teeth- not recommended in children
  - Used in Acne and some mycoplasma and rickettsial diseases, and some zoonoses
- Chloramphenicol:
  - Binds to 50s subunit; prevents peptide bond form.
  - Broad spectrum; great activity against anaerobes
  - Used only as a last resort because it can cause a fatal aplastic anemia (1 per 25,000 uses)

Types of Antibiotics, continued:

- Aminoglycosides:
  - Bind 30s subunit, stop initiation of protein syn.
  - Streptomycin, gentamicin, amikacin
  - No oral administration; relatively toxic: kidneys, hearing (even after a few days >10% hearing impairment notable)
- Glycopeptides: (vancomycin)
  - forms complexes with peptides essential to synthesis of cell wall proteins (different site from *B*-lactams, Gm+ only, cannot cross Gm- outer membrane)
  - Used to treat MRSA, endocarditis; AAPC, reserve drug
- Polypeptides:
  - Bacitracin and polymyxin - Detergent action damages membranes in Gm--, toxic to tissues - topical use-Neosporin, etc.

Antibiotics, continued

- **Macrolides: (erythromycin, clarithromycin)**
  - **Binds to 50s subunit; prevents peptide bond form.**
  - **Effective in respiratory tract infections (whooping cough, Legionnaires disease, atypical pneumonia)**
    - **new formulation, Azithromycin (Z-Pac)**
- **Lincosamides, (lincomycin & clindamycin)**
  - **Bind to 50s subunit; prevents peptide bond form.**
  - **Especially effective against anaerobes, TSS, but induces AAPC=antibiotic-associated Pseudomembranous colitis**
- **Rifampin:**
  - **Binds to RNA polymerase and blocks transcription**
  - **Used in MRSA, TB, Leprosy**

New Classes of Antibiotics:

- Quinolones: Broad-spectrum
  - Inhibit DNA gyrase
  - Examples: ciprofloxacin (anthrax) and ofloxacin
  - Expensive reserve drugs
- Penems: Broad-spectrum
  - Inhibit cell wall synthesis (POG cross-linking)
  - Nontoxic and effective at low concentrations
  - Reserve drugs

Antiviral Antibiotics:

TABLE 9-3

Antiviral Compounds

Compound	Major Viruses Inhibited	Main Clinical Use
Acyclovir	Herpes simplex	Genital and neonatal herpes
Zidovudine	Human Immunodeficiency Virus	HIV infection
Vidarabine	Herpes, Varicella	Herpes encephalitis and keratitis
Amantadine	Myxoviruses	Early treatment or prophylaxis of influenza
Ribavirin	Respiratory syncytial Viruses	RSV pneumonia in infants
Interferon	Hepatitis B	Chronic hepatitis B
Didanosine	Human Immunodeficiency Virus	HIV infection
Trifluridine	Herpes simplex	Herpes keratitis
Idoxuridine	Herpes simplex	Herpes keratitis

All are virostatic; Amatadine blocks penetration; most others inhibit viral reproduction by interfering with nucleic acid synthesis

Microbial Resistance:

- Spontaneous mutations: 1 in 10^6
- Reason for the use of multiple drugs to treat a single disease (TB)
- Spread of genetic information: R-factors
- Unnecessary and over use of antibiotics

Plasmids, pigs and chickens

- Agriculture and antibiotic resistance
  - poor policy? $ made at our expense
- Over prescription of antibiotics
  - too often for viral diseases
- we are fighting evolution
  - 1/2 bacteria produce antibiotics, others fight back; plasmid *B*-lactamase, etc
- Vancomycin was the last stand for MDR-*Staphylococcus aureus*
  - new resistant strains!

Past and Future

- 1953-1956, (the Golden-age of discovery) produced 15 new antibiotic per year
- Today:
  - isolate 10,000 new microorganisms:
    - **2,500 would be antibiotic-producers**
    - **90% (2,250) streptothricin**
    - **5% (125) streptomycin**
    - **of the rest:**
      - **40 would make tetracyclines**
      - **55 would make other known antibiotics**
      - **30 would be new antibiotics, but only 10 unique ones**
      - **9 would prove to be too toxic**
      - **1 might prove to be a useful addition**