Reasons for Slow Development of Antimycotic Therapeutic Agents

1. **Systemic fungal infections until recently have been considered rare.**
2. **Difficulty compounded by fact that both host and fungus (target) are eukaryotes.**
3. **Establishment of dependable animal models for testing antifungals has been difficult.**
4. **Economics of drug companies traditionally have been such that the cost of development and testing did not seem to warrant extensive efforts (dramatic change during last 15 years).**

Problems for Physicians Related to Antimycotic Therapy

1. **Traditional difficulties related to identifying fungal infections often deferred treatment until patient too ill to be extensively helped.**
2. **MD's selection of drug had been very limited* and confined to agents with little known modes of action****
3. **MD's reluctance to use antimycotics with serious known or claimed liabilities.**

*** until recently very small #**
**** because of small numbers of cases clinical trials difficult**

Antimycotics used most often in clinical practice

1. **Polyene macrolide antibiotics**

   major members: **a. Nystatin - 1949**
   b. Amphotericin B (Ampholiposomes) - 1956

2. **The synthetic imidazoles, triazoles and related compounds)***

   major members: **a. Miconazole - 1970**
   b. Ketoconazole - 1978**
   c. Fluconazole - 1990**
   d. Itraconazole - 1994**
   e. Terbinafine - 1995**
   e. Posaconazole - 2000**
   f. Voriconazole - 2002**
   g. Ravuconazole - (in clinical trials in U.S.)**
   h. Etc.

3. **Griseofulvin (used more in veterinary medicine today, but still used occasionally for recalcitrant dermatophytosis)**

4. **5-Fluorocytosine (often used in combination with another antifungal)**

5. **KI**

6. **Glucan synthase inhibitors (the Echinocandins or Candins)**
   a. **Caspofungin - 2001**
   b. **Anidulafungin (in clinical trials)**
   c. **Micafungin (in clinical trials)**

7. **Chitin synthase inhibitors (the Nikkomycins)**
   a. **Nikkomycin Z (in clinical trials)**

*** EBIs (Ergosterol Biosynthesis-inhibiting antifungals; azoles)**
**** Replacing Ampho B therapy in some cases; oral drugs**

1949 - Rachel Brown and Elizabeth Hazen discovered two antifungal activities associated with culture broths of *Streptomyces noursei*.

1. **Actidione/Cycloheximide***
2. **Nystatin****

both still useful.

*** inhibitor of eukaryotic protein synthesis/peptidyl transferase inhibitor**
**** anti-candidal agent (polyene structure); mainly is for treatment of cutaneous & mucocutaneous candidiasis.**

"degenerated heptaene"
6 = bonds

NYSTATIN
mycosamine (dideoxy-3-amino mannose)

Nystatin*

Nilstat - Lederle
Mycostatin - Squibb
etc.

1. **oral tablets for recalcitrant intestinal and vaginal overgrowth***
2. **powder - thrush as mouth rinse**
3. **ointment - cutaneous candidiasis e.g. Mycolog (Nystatin & Neomycin - Gramicidin - Triamei-nalone Acetonide)**
4. **topical powder - *Candida* diaper rash**
5. **suppositories - rectal & vaginal overgrowths***
6. **oral pill - intestinal overgrowth**

***Mostly replaced by azoles, triazoles, imidazoles**

heptaene
7 = bonds

Amphotericin B

1. **Traditional drug of choice for most life-threatening progressive systemic mycoses**
2. **Squibb Fungizone and Mysteclin F***
   *** with tetracycline as anti-acne and anti-candidal prep (NAS-1981 stated ineffective) (replaced by Acutane)**
3. **Supplied as microcrystals***
4. **Use prescribed mainly for progressive, potentially fatal mycoses**
5. **Must monitor glomerular filtration rates for signs of nephrotoxicity/also BUN levels, etc.**

***marketed as bile complex**

50mg Amp B
41mg Na desoxycholate **in 500 - 100 ml**
20mg Na phosphate as buffer

→ colloidal dispersion when hydrated

administered intravenously with 5% glucose sol → 0.1 mg Amp B/ml (usually in hospital setting)

Poor Correlations MIC vs Success

1. **The special nature of the disease in the host**
   i. **e.g. lg vegetations of *Candida* or *Aspergillus* on tissue**
2. **Inability of drug to penetrate some closed body cavities or granulomas (e.g. CNS during treatment of**
   ii. **cryptococcosis)**
3. **The nature of CMI system (maybe can't always help during long-term treatment)**
4. **MIC determinations may not be standardized well enough to indicate true effectiveness***

***being worked on by National Committee on Clinical Lab Standards**

Partial List of Therapeutic Successes with Amphotericin B*

1. **Essentially all cases of pulmonary and disseminated blastomycosis are now curable with adequate treatment with Amphotericin B.**

2. **About 50% of acute or disseminated coccidiodomycosis cases respond to therapy (most failures are associated with CMI failures or pregnancy)**

3. **Whereas, the mortality rate of disseminated cryptococcsis was formerly 80%, and that of cryptococcal meningitis was 100%, both are now lowered to about 30% with Amphotericin B.**

4. **About 75% of those with disseminated or chronic cavitory histoplasmosis are improved or cured by use of the drug.**

***These data are pre-AIDS epidemic.**

History of Elucidation of Modes of Action of Polyene Antimycotics

1. **increased membrane permeability noted ~ 1960**
2. **permeability induced in eukaryotes not prokaryotes**
3. **effect dependent on drug binding to eucaryotic membranes**
4. **sterols added to growth media of eucaryotic (fungal) cell protected polyene-treated organisms**
5. **selectivity of drugs (fungal vs host) arises from differences in the relative binding affinities of polyenes for ergosterol- vs cholesterol-containing membranes**
6. **fungicidal effect mainly due to proton influx (acidification?)**

Antifungal Azoles (Imidazoles and Triazoles)

1. **1970 → present - synthetic antifungals**
2. **main mode of action - inhibition of the 14α–demethylation of lanosterol in the ergosterol biosynthetic pathway**
3. **with ergosterol depleted and replaced with unusual sterols, membrane permeability is altered**
4. **membrane bound enzymes also affected**

Griseofulvin

Raistrick-

1939 = discovered in culture broths of *Penicillium* sp.
1946-47 = characterized as $C_{17}H_{17}ClO_6$

Brian -

mid 1940s = reported caused aberrant growth (curling) of *Botrytis* hyphae - "Curling factor"
1950s = tested as plant fungicide and as topical antifungal against dermatophytes
1958 = Gentles showed orally effective as anti-ringworm prep when tested in Guinea pigs

_____Therapeutic Uses of Griseofulvin

1. **Antidermatophytic agent only for particularly "refractory dermatophytosis" of humans***
2. **Modes of Action**
   a. **causes wall synthesis abnormalities (curling)**
   b. **blocks mitosis by affecting microtubule function (blocks tubulin polymerization)**
   c. **affects substrate utilization by binding with keratin**
   d. **localizes in keratinized tissue**

3. **Dosages**

children 30-50 lbs
~10 mg/da/kg
children >50 lbs
~125 - 250 mg/da/kg
Adults
~2g/da

***possibly teratogenic (some reports); mostly used now in veterinary medicine**

Flucytosine (5-fluorocytosine)

1. 1960's - synthesized as potential anticancer drug
2. 1970's - 1980's - found to have anticandida and anticryptococcus efficacy
3. Mode of action - affects RNA and DNA synthesis in fungi that have a cytosine permease, which is lacking in most filamentous fungi.

____Echinocandins or Candins

1. 1970's - Echinocandin B and aculeacin A discovered by routine screening of fungal metabolites
2. Compounds initially abandoned because of toxicity
3. 1990 - present - caspofungin, anidulofungin and micofungin entered clinical trials
4. Caspofungin approved for clinical use in 2001 for unresponsive aspergillosis; and should be approved soon for disseminated candidiasis
5. Mode of action - inhibitor of β1-3 glucan synthase so interferes with normal cell wall biosynthesis