Reasons for Slow Development of Antimycotic Therapeutic Agents

1. Systemic fungal infections until recently have been considered rare.
2. 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).
3. Establishment of dependable animal models for testing antifungals has been difficult.
4. Difficulty compounded by fact that both host and fungus (target) are eukaryotes.

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**
                   f. Posaconazole - 2000**
                   g. Voriconazole - 2002**
                   h. Ravuconazole - (in clinical trials in U.S.)**
                   I. 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
e tc.

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 - Triamcinalone Acetonide)
4. topical powder - Candida diaper rash
5. suppositories - rectal & vaginal overgrowths*
6. oral pill - intestinal overgrowth

*Mostly replaced by azoles, triazoles, imidazoles
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
   \( \Rightarrow \) colloidal dispersion when hydrated

   administered intravenously with 5% glucose sol \( \Rightarrow 0.1 \) 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 cryptococosis 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 cavitary 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

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Flucytosine (5-fluorocytosine)
1. 1960's - synthesized as potential anticancer drug
2. 1970's - 1980's - found to have anticandida and anticytrococcus efficacy
3. Mode of action - affects RNA and DNA synthesis in fungi that have a cytosine permease, which is lacking in most filamentous fungi.

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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