

In search of past time

"if we turn round to gaze into the distance of the past, we can barely see it, so imperceptible has it become."

Marcel Proust

&

Jack Bennett

What this talk is about/not about

- About: people, places and events worth remembering or knowing
- Not about: anyone in this room

Early days of medical mycology End of the 19th C



Queen Victoria ruled
1837-1901

- Physicians looking at pathology slides and noticing something different
- 16 years 1892-2008: 7 deep mycoses described: paracoccidioidomycosis (Lutz), coccidioidomycosis (Posadas, Rixford&Gilchrist), blastomycosis (Gilchrist), cryptococcosis (Busse, Buschke), sporotrichosis (Schenck) histoplasmosis (Darling), mycetoma (Wright)
- Key to discovering mycoses: knowing what's new and what's not
- Problem: finding out that the new thing was a fungus, not a parasite, and that a fungus could have two forms. Clinicians and mycologists, together.

20th Century in a nutshell

- 1914, 1937 Wars in Europe (current allies), 1950 Korea (cars, electronics), 1961 Vietnam (food, TPP), 1983 Grenada (Operation Urgent Fury, 9000 invaders/91,000 population) (13,000 medical grads), 1989 Panama (Operation Just Cause, Noriega)
- 1929 Stock market crash. Great Depression. The New Deal
- The Big Deal: 1935 Bayer. Sulfas, 1940s: Penicillin, streptomycin, etc. Corticosteroids enter clinical use
- Deep mycoses considered rare in first half of century

Mid-20th C.: the details

- Rise of medical mycology reference centers:
- Identified cultures, did research, trained researchers, ran courses, provided advice
- Pasteur Institute, Paris: Drouhet, Mariat, Segretain
- CDC: Libero Ajello, Leo Kaufmann, William Kaplan, Lucille Georg
- Columbia: Rhoda Benham
- NIH: Chester Emmons
- Duke: Norman Conant



The three musketeers of the Pasteur Institute
Drouhet, Mariat, Segretain

Respected
Admired
Liked

Pasteur became a
medical mycology
center for the world.
Now
Bertrand Dupont
John Paul Langé
Francoise Dramer
Olivier Lotholary

Mid-20th C.: more details

medical mycologists became more readily available
often trained in general mycology or microbiology

- UK: James Gentles, Phyllis Stockdale
- Brussels, Belgium: Vanbreuseghem
- Sudan: El-Sheik Mahgoub
- Germany: Fritz Staib
- Los Angeles: Dexter Howard, Milton Huppert, Victor Newcomer
- AFIP: Chapman Binford
- Basel: Hans Scholer, Pollock
- South America: Pablo Negroni, Angela Restrepo, Dante Borrelli, Juan Makimmon
- Australia: David Ellis

20th C: Second Half

- Tuberculin-like skin tests showed that coccidioidomycosis (CE Smith) and histoplasmosis (Palmer, Edwards) were common and usually resolved spontaneously
- Medical mycology books and journals began to appear: 1956 Cryptococcosis: by Littman & Zimmerman; 1958, Coccidioidomycosis: by Marshall Fieser; 1961 Sabouraudia started; 1963 Medical Mycology: by Emmons, Binford & Utz, 1964 Candidiasis: Winner & Hurley
- Medical mycological conferences began: 1956 Cocci conference, 1958 ISHAM, 1971 paracocci conference, followed later by cryptococcosis, candidiasis, aspergillosis international meetings

Discovery of polyene antifungals

- 1943 Waxman discovers first antibiotic: streptomycin produced by a soil Streptomyces
- 1944 Brown and Hazen, A chemist and a microbiologist working for the New York State Health Laboratory look for an antifungal from soil bacterium
- 1945 Streptomyces isolated from farm soil from Virginia produces antifungal: *nystatin*. The organism is named *S. noursei* (Nourses farm). Nystatin is potent antifungal and licensed to Squibb.

Brown and Hazen in their laboratory



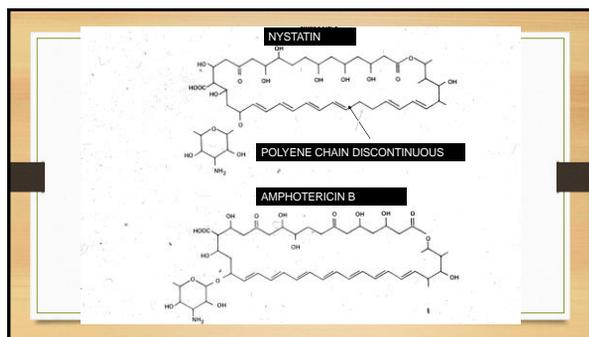
Walter Nourses farm in Virginia



- 1953 Squibb starts screening soils, finds **amphotericin B** made by a soil Streptomyces from Venezuela. Structure is very similar to nystatin. Drug is hard to purify, insoluble in water, poorly absorbed PO or IM.
- 1958 Trials start with 2-5 gm/day PO, then particulate suspension IV
- 1959 Bile salt colloidal suspension is introduced into clinical trial.

TOXIC !





More antifungals!

- 1963 Roche. "Manny" Grunberg tests a newly synthesized, failed antimetabolite, 5-fluorocytosine in murine model of candidiasis. Initial in vitro screening had found no antifungal. In proper culture medium, active in *Candida* and *Cryptococcus*. Clinical trials disappointing.
- Late 1960's: Buchel at Bayer synthesizes first azole, clotrimazole. No GI absorption. Topical.
- 1970's Janssen chemists synthesize miconazole. Poor oral absorption. IV with polyethoxylated castor oil. Hugo vander Bossche leads antifungal discovery with ketoconazole then itraconazole in 1980s.
- 1980s. Ken Richardson synthesizes fluconazole at Pfizer. Former post doc of Woodward at Harvard. Marketed in 1990. Sales skyrocket. 1999: Pfizer's global sales of fluconazole reaches one billion dollars per year, was 1/16 of Pfizer global revenue that year.

Antifungals as the 20th C ends

- 1983 Lopez-Berestein and Juliano at MD Anderson synthesized amphi into lipid complex. Less toxic. Abelcet
- 1990's: Vestar, San Dimas, Calif. Encapsulates amphi into liposomes. Higher blood levels. Low toxicity AmBisome
- 1990's voriconazole Pfizer
- 2000's posaconazole Schering Plough. Rescued by solid extrusion tablet.

Echinocandins: off to a rough start

- 1970's echinocandins discovered. Semisynthetic lipopeptides
- 1984 Eli Lilly synthesizes cilofungin. Insoluble in water. Inhibits cell wall glucan.
- 1987 Lilly clinical trials of polyethylene glycol (antifreeze) solvent. Toxicity ends trials.
- 1995 Merck finds new derivative, caspofungin, forms water soluble salt. Successful candidemia trials
- 2000's Fujisawa develops micafungin
- 2000's Vicuron develops anidulafungin. 2005 Pfizer buy Vicuron for dalbavancin and anidulafungin patents, delays development by firing everyone from Vicuron.

Advent of Multicenter Clinical Trials

- 1960s VA-Armed Forces Cooperative trials of amphotericin B
- 1971-73: MCV & UVA crypto meningitis 12/15 cured with ampho 20 mg +5FC 150 mg/kg
- 1974-76 Collaborative Cryptococcal trial ampho 0.3 mg/kg+5FC 150 mg/kg 6 wks vs ampho 0.4 mpk 10 wks. 66 pts
- 1977 NIAID Workshop on Medical Mycology Research and Training: Needs and problems: Milton Huppert, chairman. Wm Jordan, MD head of DMID. Reported lack of funding and training in the field. Most NIH funding was on nonpathogenic fungi, particularly *Saccharomyces cerevisiae*.
- 1978 NIAID sponsored the NIAID Mycoses Study Group in a series of 5 year contracts with Wm Dismukes as PI, contracts ended 2006. Unique collaboration of NIH, academia and industry. Independent annual meetings continued until 2013, then annually met with ICAAC.

Fin de siècle



- Big Pharma support reaches all-time high.
 - Clinical trials
 - Meetings and more meetings
 - Research support

then industry support started fading like the Cheshire cat, disappearing all but the grin

- Susceptibility testing becomes respectable (Frank Odds, John Rex, John Galgiani, NCCLS/CLSD)
- Collaboration among medical mycologist becomes the rule, not the exception

Looking back, what did we see?

- Effective antifungals were a major driver of support for medical mycology
- Collaborative clinical trials advanced the field (but are harder now)
- Science base began as keen observations by mycologists and clinicians
- A small number of gifted men and women trained future leaders
- It is a cautionary tale for the present: that we should seek out and nurture trainees who will follow us and keep this exciting area of science moving forward.