pre-1940 none and recognized disease often advanced to death

1940s -> 50s, sulfanamides; variable effectiveness

1960 --> Amphoteracin B; traditional drug of choice

1990 azoles?? triazoles; 1992 itraconazole drug of choice in S.A., 100mg/ for 6 mo. --> 99% clinical cure rate
Serology
- **-CF Tests**
- **-tube precipitin tests**
- **-recently ID and FA tests too**

Disease like the systemic endemic U.S. diseases being controlled with good success.

AIDS association - still rare disseminated.

***all clinically detectable cases should be treated with systemic antifungals**

Aspergillosis

An opportunistic mycosis that comprises a variety of syndromes involving a form-species of the form-genus *Aspergillus.**

Main agents:

1. ***Aspergillus fumigatus* (80%)**
2. ***A. flavus*****
3. ***A. niger*****
4. ***A. terreus***** **18-19%**
5. ***A. ochraceus***
6. ***A. nidulans***
7. ***A. clavatus***
8. **Other species ~ 1-2%**

-Cause about 5000+ hospitalizations/yr in US with > 300 deaths/yr; autopsy data* 1978 - 1982 indicated 0.5% multiorgan cases; 1980 - 1992 14-fold increase; 1993-to-date, some increase in AIDS-related cases*****
***large form-genus[+] with phialidic anamorphs; when teleomorphs/holomorphs known are Plectomycetes, Eurotiales.**
Incidence of infection 4-→38%; of fungal infection deaths, 85%.
**** next most common**
***** extremely conservative estimate**
[+]some suggest over 600 form-species (probably only about 100 "good" species)

History - very old

1815 - possibly first valid description from bird infection (most early descriptions too)

1847- 1st human case possibly Sluyter (or Bennett***, 1842)**

1850- Fresenius* - coined aspergillosis for infection due to *Aspergillus* in a buzzard (*Aspergillus*, Micheli, 1729, after aspergillum)

1856- Virchow - 4 cases → best early descriptions of bronchial & pulmonary forms – isolated *A. fumigatus*

*** named many species, including *A. fumigatus***
**** named Pityriasis versicolor**
***** worked with Berg on thrush in newborns**

1897- Renon - occupational hazard association-*
1. **pigeon handlers**
2. **handlers of moldy grain**
3. **wig cleaners**
4. **farmers working with moldy hay (Farmers' lung)**

***often chronic**

1924- Cleland - association with debilitation (opportunistic disease)

1952 until today- Opportunisitc forms most important*
1. **high % of deaths among leukemia patients/neutropenic**
2. **significant complications in organ transplant situations (e.g. BM transplants)**
3. **many outbreaks in hospital environments**
4. **AIDS**

2008. Sexual cycle of *A. fumigatus* discovered and teleomoph named *Neosartorya fumagata* (see Sz reading 8).

Clinical Syndromes Aspergillosis
Broad Classification

1. Toxicity - due to ingestion of moldy food (e.g. aflatoxicosis) (*Aspergillus* mycotoxicosis)
2. Allergy & sequelae to the presence of conidia or transient hyphal growth in body orifices (e.g. nasel & lung)
3. Colonization without invasion into preformed cavities or debilitated tissue
4.* Chronic invasive, inflammatory, granulomatous, necrotizing disease of lungs & other tissue
5.* Systemic and fatal dissemination disease

***True pathogenesis (ubiquitous & opportunistic)**

	Main Predisposing Factor	
	Neutropenia: normally	**PMNs**
oxidative micro-	**←*neutrophils* = 40-60%**	**white cell count;**
biociadal killers	**eosinophils = 1 to 3%**	**leukocytes**
no, H_2O_2, O, etc	**basophils = 0.5 to 1%**	
	lymphocytes = 20 to 40%	**T&B cells**
	monocytes = 4 to 8%	**MΦ**

Laboratory Identification

Traditionally by morphological characteristics of anamorphs

1. Colony morphology
color (most often because of spore color)
2. Conidiophore & phialide
morphology (uniserate or biserate)
3. Conidium morphology
with *A.* fumagatus
thermotolerance (45^{o}C)
other species 37-40^{o}C

Teleomorphs* (homothallic &/or heterothallic)
cleistothecial structure - pseudoparenchymatous**
Eurotiales
Eurotiaceae

***unknown for four most common pathogens**
****vs prosenchymatous of Onygenales**

Clinical Categories of "Infectous" Aspergillosis

Asthma
Allergic Alveolitis
Allergic broncho-pulmonary

A.	**Pulmonary**		
	1) allergic		
	2) colonizing (Aspergilloma)	**usually**	
	3) invasive*	**primary**	
B.	**Disseminated***		
C.	**CNS**	**usually**	
D.	**Cutaneous**	**secondary**	
E.	**Nasal**		
F.	**Iatrogenic**	**(any adverse** condition due to medical intervention)**	
G.	**Otomycosis**		

***1) due to lowered resistance caused by disease or drugs, neutropenic; granulocytopenia; (GCSF therapy)$^{+}$**
****2) barrier breaks - e.g., surgery, 3) disruption of normal flora due to antibiotics or steroids, 4) etc.**
[lots of cases initiated in operating room setting; started to show up in 1970's (or be documented)]
$^{+}$Granulocyte Colony Stimulating Factor

Pulmonary Forms of Aspergillosis

1. Allergic

a. asthma - the least serious & a response to conidia; conidia seldom germinate.
symptoms- cough, wheezing, chills, aches, pains, rare fever; no skin test reaction of arthus type (immediate*); but DTH+ detected by skin test**

b. allergic alveolitis- usually found in individuals having repeated exposure to large #s of conidia & hyphal fragments (usually occupational: farmer's lung disease)
symptoms- cough, fever, chills
- occur within 6 hrs
- X-ray infiltration common
- Arthus-type skin test***
- Repeated exposures→ granulomatous disease

c. allergic bronchopulmonary (more serious extension of allergic Alveolitis)
1) bronchoscopy may show fungus patches (rare) in bronchi
2) conidiophores and conidia often observed in lungs
3) sputum has fungus and conidia
4) positive sputum throughout disease course
5) Arthus type skin test**
6) sputum may become bloody
7) often restricted to upper lung lobes

***IgE-mediated or immuncomplex type**
****CMI-mediated or immuncomplex type**
*****2 - 4 hrs., & mediated by ppt antibodies (see notes p24)**

2. Colonizing aspergillosis (aspergilloma)
a. development of large fungus balls* throughout lungs or cavities caused by other disease
b. symptoms as above - but more severe

*** can inhibit exhalation/often associated with TB**

3. Invasive pulmonary aspergillosis
- rare form - fungus wide-spread
- usually opportunisitic
- pneumonia, fever, cough, pain
- extensive X-ray
- often in cancer patients with leukemia and lymphomas
- may be chronic or sometimes fulminate

4. Disseminated
- symptoms of acutely ill patient
-lung> brain> kidney >heart>etc.
- lung origin
- hyphae in tissue dichotomously branched and nonsporulating

5. CNS mostly from iatrogenic invasion (drug addicts)
- acute meningitis
- rapidly fatal disease

6. & 7. Cutaneous & nasal (rare)

8. Iatrogenic - very common & often symptoms as with disseminated

9. Otomycosis = colonization of ear drum external surface (swimmer's ear), bacterial overgrowth common → much discomfort.
- antibacterial treatment only gets rid of bacteria; fungal origin still there:. Can be treated with topical antifungals.

Aspergillosis - Prognosis & Therapy

Allergic - essentially benign; needs little attention or antiallergy treatments (steroids, desensitivation, Allegra™, etc.)

Colonizing

colonizing may or may not require intensive antifungal therapy if in otherwise healthy patient
- need to minimize bronchial plugging (asperation; lavage)
- surgical resectioning

Invasive:

-Amphotericin B; various azoles in use or in trial, itraconazole most promising
-Granulocyte Colony Stimulating Factor (G-CSF) therapy

Serology

CF, CIE, ID*

Factors for Successful Treatment of Aspergillosis*

1. **Early recognition of disease**
2. **Prompt, aggressive therapy with FUNGIZONE® (amphotericin B/Squibb)****
3. **Supportive measures continued until granulocyte recovery**

***Burch JA: J Clin Oncol 5 (12): 1985-1993, 1987**
****Some patients included in this study also received flucytosine**