Cryptococcosis*,**, Syn of Cryptococcosis
Busse - Buschke's disease
European Blastomycosis
Pigeon's disease
(Pigeon breeders'disease)

*usually considered to be an opportunistic mycosis that often becomes systemic.

**remains the most common fatal infection involving the central nervous system in patients with AIDS

History

Busse (1894) & Buschke (1895)
first reported isolation of fungus from human disease (tibia of human female).

Sanfelice - described encapsulated yeast isolated from nature which caused infections in animals
- Saccharomyces neoformans (1895)

Vuillemin - determined fungus was not ascosporic. Therefore, imperfect and illegally assigned to Saccharomyces. Renamed in 1901 B & B's fungus as Cryptococcus hominis (hominis illegal) & Sanfelice's as C. neoformans.

Kreger - Van Rij (1952) with Lodder
stabilized anamorph name as C. neoformans (Sanfelice) Vuillemin; based on work of Benham et al.

Benham et al (1950's) (also Lodder) determined:
1) only 1 species most likely
2) 4 serotypes - antigenic nature of capsular polysaccharides (GXM = glucouronoxylomannans);

serotypes A,** B,+ C,+ D* (AD new, 2000, so now 5 serotypes)
3) blasto & crypto different diseases
4) serotypes A & D associated with pigeons

Howard, Kwon Chung, Bennett, etc. (1960's to 1990's)
** = var grubii A (95% US isolates); (post 1980's, mostly A with AIDS in US)
* = var neoformans D (other temperate regions)
+ = var gattii B (5% US isolates) & C (tropical & subtropical)
- established some correlations between serotypes & ecological & geographical distribution

Shadomy (1970) clamps & dolipores (see Kwon-Chung & Bennett, P. 432)

Kwon Chung (1975) Filobasidiella teleomorph

Ellis & Pheiffer (1990) var gattii
sero B isolated from Eucalyptus camaldulensis in Australia and then U.S.
Importance of discovery of *C. neoformans* teleomorph

1. clarified many aspects of "unusual" biology of this form-species
2. clarified why serotypes might be geographically correlated and environmentally localized
3. appeared to clarify why pigeon handlers and breeders in particular seemed to have propensity for pulmonary disease prior to onset of cryptococcosis
4. suggested smaller size of basidiospores vs yeasts might also often initiate infections, although dried, dehydrated yeasts* usually thought to initiate infection to be phagocytized in lungs

*dried yeast are very much smaller than rapidly growing, hydrated yeasts.

---

### Teleomorph

<table>
<thead>
<tr>
<th>Filobasidiella neoformans</th>
<th>Basidiomycota</th>
</tr>
</thead>
<tbody>
<tr>
<td>var. neoformans</td>
<td>Phragmobasidiomycetes (?) teleomorph</td>
</tr>
<tr>
<td>var. bacillispora</td>
<td>Class &amp; Order</td>
</tr>
<tr>
<td></td>
<td>controversial</td>
</tr>
<tr>
<td></td>
<td>Tremellales</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>Filobasidiales ?</td>
</tr>
<tr>
<td><em>C. neoformans</em>**</td>
<td>caffeic acid &amp; phenol oxidase →</td>
</tr>
<tr>
<td>(anamorph)</td>
<td>brown colonies</td>
</tr>
<tr>
<td>var</td>
<td>assimilation</td>
</tr>
<tr>
<td>grubii var. (2001) sero A</td>
<td>malate</td>
</tr>
<tr>
<td>neoformans (1975) sero D</td>
<td>--</td>
</tr>
<tr>
<td>(sero *A &amp; D)</td>
<td>color change</td>
</tr>
<tr>
<td>Temperate</td>
<td>CGB* or GCP</td>
</tr>
<tr>
<td>A, mainland U.S.</td>
<td>growth</td>
</tr>
<tr>
<td>gatti (1989)</td>
<td>37-39°C</td>
</tr>
<tr>
<td>(sero *B &amp; C)</td>
<td>+</td>
</tr>
<tr>
<td>Tropical &amp; Subtrop.</td>
<td>blue*</td>
</tr>
<tr>
<td>B &amp; A, So. Cal.</td>
<td>or</td>
</tr>
</tbody>
</table>

*creatine, glucose, brom thymol blue agar
**glycine, cycloheximide, phenol red agar
*** capsulated yeast Blastomycetes (form-class)
Clinical Forms of Cryptococcosis

Primary Pulmonary vs Opportunistic*

1. Pulmonary
   a. Primary forms in normal hosts rapidly resolved with minimal symptoms (often subclinical).
      -probably initiated by inhaling basidiospores or dried yeasts in low numbers. No evidence exposure yields long-term immunity. Inhalation of larger numbers of yeasts or spores* may yield acute symptomatic infections with infrequent spread to other body sites (CNS).
   b. chronic forms of pulmonary** infection w/o spread or slow spread yielding cutaneous or meningitic involvement.
   c. Treatment of chronic pulmonary cryptococcosis
      Ampho B alone (or with 5FC)
      surgical removal of lung lesions
      fluconazole following failure with 5FC and/or Ampho B
      other azoles*(Diflucan)

2. Opportunistic forms++
   a. pulmonary
   b. CNS (most diagnosed form)
   c. cutaneous (rarely primary)
   d. mucocutaneous
   e. osseous
   f. visceral

Opportunistic forms also initiated as pulmonary disease in compromised hosts.

Main type of disease known for about 1st 50 - 60 years of study of cryptococcosis.

Case ranges from 200 - 300/year of cerebral meningitis in U.S. to 15,000 subclinical cases in New York City/year.

1982 hospital release data estimates 1,200/year with ~200 deaths (pre-AIDS)
-mainly diagnosed as meningitis or CNS disease because pulmonary form difficult to diagnose.

1990 to present: Cryptococcus neoformans is currently the most commonly isolated pathogen from CSF in U.S.
The vast majority of persons with cryptococcal meningitis have AIDS. (Most common CNS fatal infection)

Two-thirds of all cryptococcosis cases are AIDS related, although other populations (renal transplant recipients, diabetics, and those with hematologic malignancies) are at risk. (Today)

About 10% of AIDS patients will develop cryptococcal meningitis; percentage may increase as survival is prolonged among AIDS patients (due to immunosuppression, use of antipneumocystis prophylaxis and antiretroviral therapy, etc.)

Today, 4th most commonly recognized cause of life-threatening infection in AIDS.
Relapses after successful treatment of cryptococcal meningitis among AIDS patients is common.
Successful retreatment among AIDS patients who relapse their cryptococcal meningitis is rare and most patients die from the cryptococcosis.
With cryptococcosis and AIDS, the concept of indefinite suppressive therapy has emerged as a viable strategy.

Fluconazole and Amphotericin B are relatively effective agents for prevention of relapse cryptococcal meningitis in AIDS patients (relapse rates: 12 of 78 with Amphotericin B versus 2 of 111 and 1 of 34 with fluconazole). Itraconazole is also effective.

* All forms of active cryptococcoses must be treated to prevent more serious disease or death.
**often from long-term repeated exposure to relatively low doses of infecting agent (pigeon breeder's disease)
*probably all initiated by inhaling spores/yeasts (dried)
++often associated with collagen diseases, also lupus erythematosus, sarcoidosis, neoplasias, bushing's syndrome & AIDS
Risk Factors for Cryptococcosis*:

- HIV infection
- Chronic corticosteroid therapy
- Organ transplants
- Chronic leukemias and lymphomas
- Sarcoidosis


Factors for Successful Treatment:

1. Prompt diagnosis
2. Intensive treatment with amphotericin B (6 to 10 weeks)/selected EBI fluconazole
3. A suppressive regimen for high-risk patients
4. Control of the underlying disease

Symptoms and Clinical Pictures

1. Pulmonary (Primary)
   a. mostly asymptomatic
   b. symptomatic
      - cough
      - low-grade fever
      - pleuritic pain
      - weight loss (some)
      - little productive sputum
      - nonlocalized lung lesions
      - resolution \( \Rightarrow \) few residual scars of past lesions
      - X-ray picture very variable
      - definitive identification of disease depends on isolation of organism and/or latex agglutination test for cryptococcal antigen or fluorescent antibody of biopsy

2. Cutaneous (primary - rare)
3. Opportunistic

CNS Cryptococcosis
1. most commonly diagnosed form of disease

2. before Ampo B, disease considered to be uniformly fatal (now ~ 6-10% & getting better even as related to AIDS))

3. main early presenting symptoms
   - headache
   - possibly slight fever
   - confusion

4. brain may have multiple or single lesions \(\rightarrow\) cryptococcal granuloma
   - nausea
   - coma
   - vomiting
   - paralysis
   - mental changes
   - death

Cutaneous and Mucocutaneous

1. indicative of dissemination
2. pustular lesions or abscesses
3. represent about 5 to 15% of patients presenting with cryptococcosis today

Osseosis (bone involvement)
1. about 10 – 15% of cases
2. very difficult to diagnose
   X-ray indication together with other evidence for disease (CT)

Visceral
1. any organ or tissue (CT)
2. extremely serious

Prostate
1. persistent focus in some patients after "successful" antifungal therapy
Detection of CNS Cryptococcosis

Spinal Tap
1. increased pressure due to fluid accumulation
2. clear fluid
3. cell count somewhat elevated
4. sugar is very low
5. organisms sparse or numerous - usually spun to concentrate and examined microscopically after staining with India ink for capsular yeast
6. L.A. test, IFA sometimes

Other CAT (computerized axial tomography) scans & MRI (magnetic resonance imaging) scans helpful, but generally only suggestive of brain/spinal cord problems.

Clinical Forms of Cryptococcosis

Serodiagnosis
Primary tool for diagnosis

1. Pulmonary
   LA Test
2. CNS
3. Cutaneous****
   LA Test
4. Mucocutaneous
   +
5. Osseous
   IFA*
6. Visceral
   TA**

* Latex agglutination test; 90-95% accurate for CNS; titers>1:8 indicative of active infection; detect polysaccharide antigens
** IFA; Indirect Fluorescent Antibody test
*** Tube Agglutination test; carried out with capsular polysaccharide antigens.
**** rarely primary