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Fungal Infections

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Fungal infections have increased in frequency in the last decades because of the growing number of immunocompromised patients who survive longer periods of time than in the past, the widespread use of immunosuppressive drugs, a large aging population with increased numbers of malignancies, and the spread of AIDS. Although fungi are present everywhere, some mycoses predominate in the tropics, not only in view of warm temperature and humid climate, which favor their growth, but also because of inadequate hygienic and working conditions brought about by poverty.

Mycotic diseases in the brain are usually secondary to infections elsewhere in the body, usually the lungs, less often from other extracranial sites, and in the vast majority of the cases spread via blood circulation. Only occasionally they result from direct extensions from infections of the sinuses or bone, and less frequently from prosthetic heart valves. Candida may be endogenous in origin, inhabiting the digestive tract. Most fungi cause basal meningitis or intraparenchymal abscesses. Direct extension from the cribriform plate cause necro-hemorrhagic lesions in the base of the frontal lobe.

Although fungi are common in our environment, few are pathogenic. In this paper mycotic infections are divided into opportunistic and pathogenic; although most of the latter have also been described in immunosuppressed patients, some of those caused by opportunistic organisms, have also occurred in the absence of predisposing factors.

Introduction

Although fungal infections of the nervous system have been known for a long time, their increase in frequency in the last decades has been favored by the growing number of immunocompromised patients who survive long periods, the widespread use of immunosuppressive drugs, by a larger ageing population with an increased number of malignancies, and the spread of AIDS (6). These infections are usually secondary to hematogenous dissemination from a focus elsewhere in the body, most often pulmonary or intestinal or, to a lesser extent, from other extracranial sites. Occasionally, they result from direct extension from infections of the sinuses or bone. An additional source of infection is represented by prosthetic heart valves. The site of entry, however, may remain unrecognized and cases have been reported in which the only evidence of infection was in the CNS (78).

Soil and vegetation are the usual source of fungal infections. Only occasionally can they be acquired through inhalation of dust or through puncture wounds. Candida may be endogenous, inhabiting the digestive tract and vagina (78).

Morphologically fungi in tissue may appear as: a) yeasts up to 20 μm in diameter (Blastomyces, Candida, Coccidioides, Cryptococcus, Histoplasma, Paracoccidioides, Sporotrichum, Torulopsis), b) variable size of branching (septate) hyphae (Aspergillus, Cephalosporium, Cladosporium etc), or c) nonseptate or pseudohyphae of intermediate size, which are larger and more irregular than yeasts, although smaller than true hyphae (Candida, Absidia, etc). According to the type and size of the organism involved, lesions in the CNS have different appearances. The smallest forms (yeasts), reach the capillaries, producing leptomeningitis; they have access to the cerebral microcirculation from which they infect the subarachnoid space. The large hyphae obstruct large and intermediate arteries and give rise to extensive infarcts such as in aspergillosis and mucormycosis. Pseudohyphae, such as those of *Candida*, occlude small blood vessels in the microcirculation, producing adjacent tissue necrosis that rapidly converts to microabscesses. As the infection persists, granulomatous inflammation occurs in adjacent leptomeninges, neural parenchyma, or both. For the identification of fungi in tissue sections, certain staining techniques are of considerable value such as the periodic-acid-Schiff method (PAS) and methenamine silver. Immunocytological methods have also proved very helpful (39,78).

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Although fungi are common in our environment few are pathogenic such as *Blastomyces dermatides, Paracoccidioides brasiliensis, Pseudallescheria boydii* and *Coccidioides*. They are capable of provoking disease in the absence of known predisposing factors. However any fungus is potentially a CNS pathogen. Many patients with fungal infections have some degree of immunosuppression. The type and extent of reaction will depend on the underlying immunologic status of the patient. Suspicion of unusual infections including the obscure mycoses should be maintained for any compromised patient.

The following presentation is divided in opportunistic and pathogenic fungi, although most of the latter may also act as opportunists and some of the so-called opportunists have also occurred in the absence of predisposing factors.

Although only few mycotic diseases are exclusively tropical, some of them are predominant in these regions where they found ideal climatic conditions for their development. In addition, poverty, poor working conditions and the habit to walk bare foot provides additional conditions for the spreading of mycoses.

An additional drawback of fungal infections is their resistance to available treatments. Treatment of choice is amphotericin B, whilst the role of azoles (ketoconazole, fluconazole) and sulphonamides should be evaluated (4)

Opportunistic Fungi

Aspergillosis. This infection usually takes place in debilitated hosts and is caused by organisms that are usually saprophytic. Predisposing factors include corticosteroid and immunosuppressive therapy, prolonged antibiotic use, neoplasms (especially lymphomas and leukemias), collagen disorders, diabetes *mellitus*, chronic pulmonary disease, organ transplantation, neutropenia, hepatic failure, chronic lung disease, cavitary tuberculosis, cardiovascular surgery, alcoholism, intravenous drug abuse, marijuana use, general malnutrition, and age (1, 32, 35, 70). On the other hand, in AIDS patients aspergillosis is seen only occasionally (40, 45, 46, 54).

Several species can cause CNS infection, but most cases are due to *Aspergillus fumigatus* or *Aspergillus flavus*, which are found in soil, plants and decaying matter. They have a worldwide distribution and consist of branching septate hyphae, varying from 4 to 12 μm in width. Multiple septa are seen at regular intervals, and hyphal branching form acute angles in the same direction as the main hyphae (39, 78).

Most human infections occur initially in the lung. CNS involvement is usually the result of hematogenous dissemination from the lungs (6, 39, 78) or gastrointestinal tract (90); however, some cases are due to extension from the paranasal sinuses (76, 84, 86, 87) ears, skin and adnexa, or the result of head trauma. The infection may also spread to the CNS from the orbit (30), nose, and may be due to actual invasion and erosion of the bone plate of the cranial base, to extension through some anatomical orifices as the cribriform plate (34) and optic foramen, or to spread along anastomotic vessels that communicate the cranial cavity and the orbit or sinuses by way of the ophthalmic vein. Open heart surgery and major vascular surgery provide another portal of entry for the disease.The possibility of inoculation through exchange transfusions, rectal fistula, the uterus after a septic abortion, and traumatic injuries, have also been suggested. In some cases, however, no evident source of infection has been found (47).

Aspergillus disseminates via the hematogenous route and seems also able to spread along lymphatics, as well as through the airways. It has a marked tendency to invade arteries and veins, producing a necrotizing angiitis, thus setting the stage for its hematogenous spread. The organs most frequently involved by metastatic propagation are the heart, brain, kidneys, gastrointestinal tract, liver, thyroid, and spleen.

Manifestations of cerebral aspergillosis are related to the onset of focal neurologic deficits that commonly involve areas supplied by the anterior and middle cerebral arteries (39). The clinical picture depends predominantly on whether the disease is primary or metastatic and on the location, extent and character of the lesions. In some cases the clinical picture is that of a space-occupying lesion or an abscess. The symptoms and signs most frequently encountered are headache, hemiparesis, and convulsions, but there are often fever, paralysis of cranial nerves, and abnormal plantar reflexes. Sometimes there is blurring of the optic discs, vomiting, coma, and other signs of increased intracranial pressure. In other instances, the clinical picture is that of a meningitic process. The neurologic signs are often nonspecific (4).

Direct examination and cultures are the techniques most frequently used in the diagnosis of the disease. There is spinal fluid pleocytosis of under 600 cells/cu mm. The protein level is only moderately elevated, and the sugar content is normal. Organisms are usually not found in CSF and the diagnosis of CNS involvement is infrequently established during life (4).

Neuropathology. The morphological changes observed in aspergillosis of the CNS vary according to whether the infection is the result of hematogenous dissemination or of local spread. In the first event, the process generally leads to multiple lesions which involve areas of the anterior and middle cerebral arterial distributions, and tend to be acute and necrotizing or purulent. In the latter they may be chronic and have a tendency to fibrosis and granuloma formation. They may involve the cerebral cortex,

white matter, and basal ganglia. Mycotic aneurysms due to Aspergillus have been reported (11)

The fungus is highly angiotropic, and the lesions are often foci of hemorrhagic necrosis that resemble hemorrhagic infarcts. They convert into septic infarcts with associated abscesses and cerebritis. They vary in size between 0.1 and 2.5 cm, although some may reach 4 or 5 cm. A thick fibrous capsule is seen only in rare instances. Necrotizing non-suppurative lesions are described as white or yellow multiple foci of necrosis with a hemorrhagic component, measuring from a few millimeters to several centimeters (6, 39). Much less frequently the fungus produces intraparenchymal granulomas or even meningitis. Granulomas may be circumscribed as in the cases reported by Jackson et al (36) in which the gasserian ganglion, the lesser wing of the sphenoid bone, the cribriform plate, the branches of the ophthalmic division of the trigeminal nerve and the intracranial portion of the optic nerve were involved. The cerebellar hemispheres are likewise frequently affected.

Histologically, the most striking feature is the intensity of vascular invasion with thrombosis. The amount of inflammation varies according to the stage of the disease and from patient to patient, neutrophils predominating in the early phases whilst treated cases show scant inflammation. In abscesses, frank pus can be seen in the center of the lesion and abundant neutrophilic infiltration at the edges, sometimes accompanied by giant and epithelioid cell granulomas. Granulomatous lesions consist of aggregates of lymphocytes, plasma cells and epithelioid cells with variable amounts of collagen and necrotic tissue. Multinucleated giant cells of the Langhans type may also be present as well as fungal hyphae. As in abscesses, blood vessels are always involved and may show thrombosis and invasion of the wall by fungi (78, 90). The meninges overlying both abscesses and granulomas show variable amount of exudate. Lesions of necrotizing nonsuppurative type consist of an area of coagulative necrosis with variable amounts of neutrophilic reaction and hemorrhage.

In tissue the organisms form dichotomously branching septate hyphae, faintly visible with hematoxylin and eosin stain and are often weakly stained with the PAS. They are most readily demonstrated with methenamine silver stains. Because of the similarity to certain other hyphal organisms, only a diagnosis of "tissue invasive septate hyphae, consistent with aspergillosis" can be rendered by histopathology alone (6).

Treatment in invasive aspergillosis includes amphotericin B associated, in certain cases, with flucytosine.

Mucormycosis. Although still uncommon, mucormycosis of the nervous system is being encountered more frequently. In the brain, it is a unique disease widely observed in the United States and often associated with diabetic ketoacidosis (63) and intravenous drug abuse (24, 33, 69). This acute fulminating disorder is caused by direct invasion or hematogenous spread of nonseptate irregular hyphae to the CNS. It occurs in the rhinosinoorbital region, pulmonary areas and gastrointestinal tract, as well as a focal or disseminating disease in the skin.

Mucormycosis is caused by several genera that belong to the family Mucoraceae, such as *Rhizopus, Mucor*, and *Absidia* mainly the first (95% of the cases), which includes *Rhizopus arrhizus* and *Rhizopus oryzae*. They consist of filaments or stolons from which root-like structures or rhizoids grow and are characterized by broad, branching, non-septate hyphae, measuring 6 to 15 µm in diameter and up to 200 µm in length. Hyphae may be seen singly or, often, in clusters. From the rhizoids, sprouts (sporoangiospores) bearing sacs (sporangia) develop. The organisms are ubiquitous and are found in the soil, manure and decaying vegetation material and are frequently airborne (39, 78).

Several patterns of the disease with somewhat different predisposing conditions have been delineated (72). Unlike most other mycoses, in which cerebral involvement is secondary to a primary focus in the lung, this mycosis develops most frequently from an infection of the skin of the face or in the mucosa of the nose and nasopharynx, and spreads to adjacent regions and to arteries within the orbit and the internal carotid arteries, with eventual thrombosis (78). The infection may involve the sphenoid sinus and the bone of the floor of the sella may be necrotic (22). The frontal lobes are involved by direct venous invasion through the orbital plate. Diabetic patients, who are particularly susceptible to infection - the predisposing factor being acidosis rather than, hyperglycemia - develop, in the majority of the cases, the rhinocerebral form of the disease.

When brain involvement results from hematogenous dissemination from extracranial sites such as the lungs and the gastrointestinal tract, it is associated with predisposing conditions such as acidosis from diarrhea and dehydration in children, organ transplantation, immunosuppressive therapy for hematologic malignancies, and intravenous drug abuse. It often follows treatment with corticosteroids, antibiotics, and cytotoxic drugs (6, 39, 69). A few cases have been reported in association with AIDS, but some of these patients were also drug abusers (16, 51).

Although these fungi have been considered opportunistic, the cerebral form of the disease has also been described in previously healthy individuals (34, 50).

In its rhinocerebral form this mycosis extends rapidly to the orbit, where it produces unilateral ophthalmoplegia, proptosis, edema of the lids, corneal edema, and, occasionally, blindness. Headaches, nuchal rigidity, and convulsions may result from

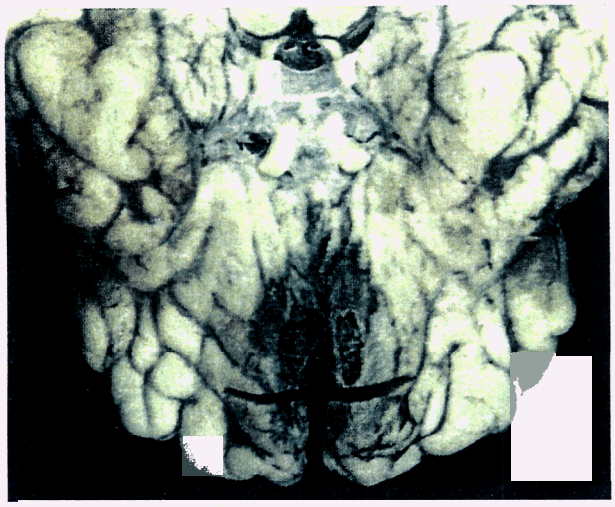


Figure 1. Rhinocerebral mucormycosis. Hemorrhagic necrosis of the medial orbital region of the frontal lobes.

meningeal infiltration and subsequent extensive vascular lesions result in aphasia, hemiplegia, lethargy, disorientation, and coma. The illness often runs an acute, often fulminating, course, with death within a few days (4). Although the prognosis in this infection is usually poor, improvement can occur after treatment of the diabetic ketoacidosis. Likewise, aggressive surgical extirpation combined with antifungal agents have aided these patients.

The diagnosis can be suspected when the disease occurs in patients at risk but must be confirmed by examination of the biopsied nasal material or scrapings from the affected antrum (4). The characteristic hyphae are diagnostic. The spinal fluid is under normal pressure but may be stained with blood. Usually a minimal pleocytosis occurs, although as many as 40,000 leukocytes/cu mm have been reported. The spinal fluid protein and sugar values are elevated (4).

Neuropathology. Necrotic hemorrhagic lesions occur at various sites in the brain, but mainly at the base of the frontal lobes (Fig. 1). When CNS involvement results from hematogenous dissemination, the lesions often produce hemorrhagic necrosis in deep gray nuclei (33, 82). Thrombosis of the cavernous sinus and carotid artery commonly occurs.

The fungi are highly angiotropic and appear as broad nonseptate hyphae, around and within the walls of blood vessels in the meninges and brain, obstructing blood vessels, causing thrombosis, associated with extensive hemorrhagic infarction of the brain tissue (66), and extending into adjacent damaged tissue with a mixed, or predominantly neutrophilic inflammatory response, which may be absent in areas of infarction. Occasionally, multinucleated giant cells are present, but granulomas are not typically encountered (6). The organisms are relatively well shown with H&E (Fig 2), but can be demonstrated better with PAS and methenamine silver stains (Fig. 2).

Amphotericin B, trimethoprim and sulphametoxazole are used in this mycosis; control of diabetes is also an important measure

Candidiasis. Candidiasis (moniliasis, candidosis) has become a common mycotic infection of the CNS (64). The most common variety of the disease is thrush, or infection of the mucous membrane of the oral cavity or vagina. Less commonly, however, the skin and any visceral organ may be affected.

Candida species are normally found as saprophites in the digestive, genital, and cutaneous flora, especially the oral cavity and esophagus from where they may invade submucosal vessels and disseminate hematogenously. The portal of entry of the fungus may also be intravenous, when therapeutic or recreational drugs are administered by this route. Several cases have followed open heart surgery. A large number of cases of septicemic candidiasis have been described arising as a complication of other diseases or their treatment. A wide variety of conditions promote hematogenous dissemination. These include long-term antibiotic and corticosteroid therapy, indwelling catheters, hyperalimentation lines, abdominal surgery, diabetes, burns, malignancies, neutropenia, intravenous drug abuse and AIDS (6, 26, 46, 78). However, there are cases in which involvement of the brain occurs in previously healthy persons (48).

Candida organisms are found world wide, and usually present as pseudo-hyphae with periodic constrictions at septations points, chains of elongated cylindrical cells and oval budding cells 2-3μm long. These pseudohyphae represent a succession of individual cells and are distinct from true hyphae or filaments, which do not have these "pinching" points at septa. In candidiasis, pseudohyphae are associated with 2-3 μm oval spores or blastospores which can be seen in deep tissue or on surface linings. Blastospores are spherical or slightly oval; all other *Candida* species are more oval or elongated (39).

The CNS is only occasionally involved, usually by hematogenous dissemination from a primary focus elsewhere in the body. Septicemia and endocarditis have been reported. Postmortem studies have established that candidiasis is a common fungal infection in the CNS (64) and that cerebral lesions occur late in cases with visceral candidiasis (65). Candida meningitis can occur spontaneously, as a complication of disseminated candidiasis or as a complication of neurosurgery (61), via direct inoculation of the organism into the CNS, an infected wound or ventriculostomies (10, 49, 75).

The clinical symptoms and signs of CNS candidiasis are those of a low grade meningitis. The cerebrospinal fluid pressure is usually increased and shows mild lymphocytic pleocytosis and a mild increase in protein level. The diagnosis is established by the identification of the organism (4)

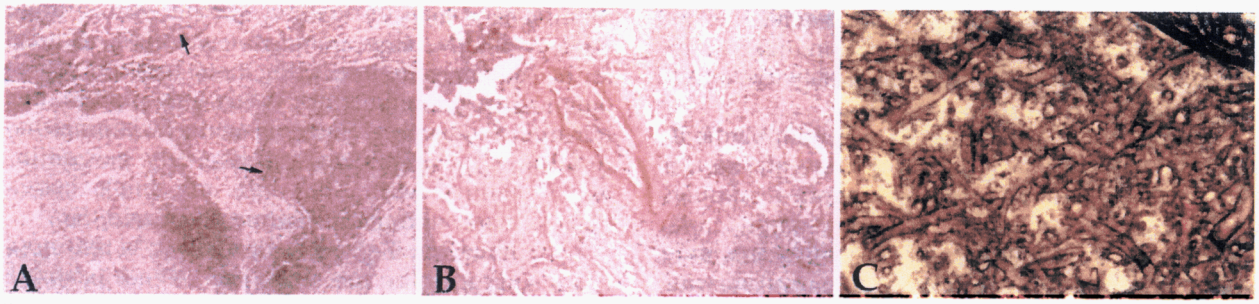


Figure 2. Rhinocerebral mucormycosis. (**a**) Leptomeningeal and superficial cortical hemorrhage and intravascular fungal hyphae (arrows). (**b**) and (**c**) Broad irregular hyphae infiltrating the vessel wall and invading the adjacent tissue. a - H&E x 85, b- PAS x 40 (on slide), c- methenamine silver x 100 (on slide).

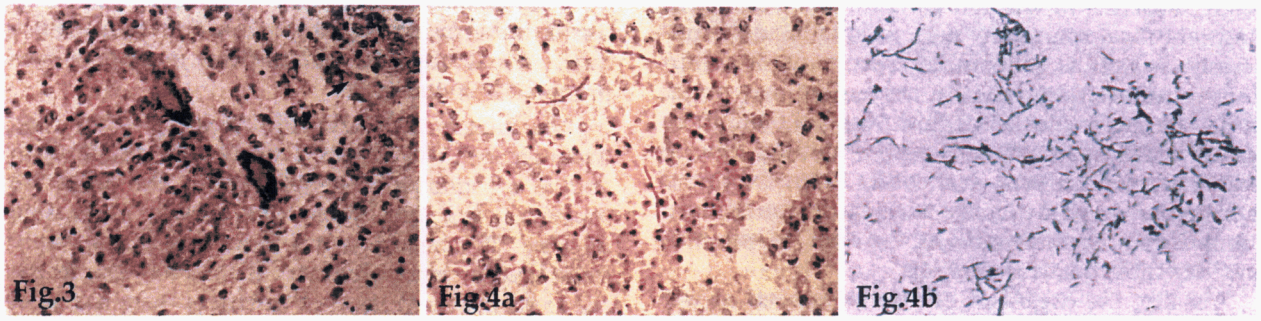


Figure 3. Candidiasis. Candida granuloma containing two multinucleated giant cells. Hyphae are faintly stained with H&E (arrow). H&E x 180.

Figure 4. Candidiasis. Hyphae and yeasts are well demonstrated with PAS (**a**) and methenamine silver (**b**). a - x 180, b - x 65.

Neuropathology. Gross lesions may not be apparent. Involvement of the nervous system is usually in the form of multiple microabscesses that may be accompanied by microgranulomas. The microabscesses can involve any part of the CNS, although they are more frequent in the distribution of the anterior and middle cerebral arteries (39). In the early stages they have the appearances of hemorrhagic infarcts. Subsequently they become abscesses and granulomas without central foci of necrosis. Additional infarcts may occur as result of thrombosis of small blood vessels caused by filaments and budding organisms (65).

Histologically, the meninges contain a slight lymphocytic infiltration. Both the grey and white matter of the brain may contain acute abscesses, a granulomatous lesion (Fig. 3), or merely perivascular cuffs of lymphocytes. Both yeast forms (blastospores) and pseudohyphae of *Candida* are encountered in the lesions. They may be faintly basophilic when stained with H&E but are intensely stained by the PAS (Fig 4a) and methenamine silver reaction (Fig. 4b). The cellular reaction around the fungus is variable, and there may be no reaction. It consists of lymphocytes, plasma cells, a few polymorphs and occasional giant cells. On occasion, the lesions may resolve.

Recommended treatment consists of amphotericin B and 5-fluorocytosine.

Pathogenic Fungi

Coccidioidomycosis. Coccidioidomycosis is a geographically restricted mycosis, which include regions of semi-arid climate. Its distribution corresponds to areas where warm temperatures and dry conditions exist (81). It is endemic in the southwestern United States (especially in San Joaquin Valley and Arizona), Mexico and South America (particularly Argentina and Paraguay) (78). Both mycelia and spores are carried a considerable distance by wind or transported by rodents (5).

The causative organism, *Coccidioides immitis*, is a nonbudding spherical structure measuring 20-70 µm in diameter with a double refractile capsule. Mature forms are filled with numerous small (2-5 µm in diameter) endospores. This structure is easily recognized on routine H&E stains. The endospores are released into the tissue after the spherules rupture (39).

Inhalation of spores through infected dust frequently leads to self-limited pulmonary infections. Lesions may arise in the absence of underlying disease, although occupations that are associated with large amounts of dust predispose to the disease. The fungus is considered both a pathogen and an opportunist, a number of cases having been reported in patients with AIDS (23, 46, 56). It has been estimated that disseminated disease develops in less than 0.2% of these patients (6) and that it occurs more often in the non-white population and in pregnant, diabetic,

or immunosuppressed persons. Involvement of the CNS occurs in about one third to one-half of the cases via the hematogenous route, usually as a terminal event (66).

The infection initially produces a mild febrile illness followed, in a number of cases, by infection in the lungs. This leads to the formation of nodules which may calcify with minimal lymph node response. Primary infection of the skin occurs more rarely. Coccidioidomycosis of the central nervous system usually becomes apparent 1 to 3 months after the primary infection or during the course of a disseminated illness. It manifests itself chiefly as an acute, subacute, or chronic symptomatic meningitis. Transient focal symptoms such as aphasia and hemiparesis, as well as generalized complaints of confusion, restlessness, and mental depression, may occur. If the meningitis blocks the flow of spinal fluid, there results acute hydrocephalus with vomiting, intense headache, papilledema, and coma. Extensive spinal meningitis or granulomas may cause spinal cord compression. Osteomyelitis of the skull or vertebrae may be visible on x-ray film (4).

Usually, the organism can be recognized in wet preparations of the CSF, which can show endo-sporulating spherules and scattered free endospores. Changes in the CSF closely resemble those occurring in tuberculous meningitis. Usually the fluid is under increased pressure. It may appear clear, turbid, or xanthochromic. The cell count averages several hundred per cubic millimeter, but it may be as high as 3000/cu mm and consists predominantly of lymphocytes. Complement fixation tests on serum are helpful for the diagnosis.

Neuropathology. Neuropathological findings vary with the duration of the meningeal involvement. An exudate accumulates in the subarachnoid space. Thickened, cloudy, opacified leptomeninges, with small nodules (caseous granulomata), are most pronounced at the base but can also occur in the cervical cord region. The exudate may become organized, leading to fibrosis and subsequent obstructive hydrocephalus. Coccidioidal meningitis tends to involve particularly the sulci and is usually rather unimpressive to naked eye examination. Involvement of the blood vessels may also be observed and multiple aneurysms may follow. The disease can spread to the brain tissue. Granuloma formation is a rare occurrence and consists of large lesions within the brain and, occasionally, the spinal cord. Brain changes secondary to meningitis, namely multifocal encephalomalacia, may be conspicuous. However, gross coccidioidal lesions of brain parenchyma are most unusual (27, 37, 56).

Histologically, the meningeal reaction resembles that of a tuberculous infection and is characterized by organisms surrounded by epithelioid cells, giant cells, lymphocytes and plasma cells; small abscesses with caseous necrosis are also observed and vascular involvement may be striking. In the tissues fungi form distinctive large sporangia (spherules). As long as the sporangia are intact, the tissue reaction is predominantly granulomatous. When they rupture, the released endospores elicit an acute inflammatory reaction. The organisms are generally basophilic when stained with H&E but are much better demonstrated with methenamine silver stain (56).

Amphotericin B given intravenously is the most promising drug for this infection. When localized compression of the spinal cord exists, attempts to remove granulomatous tissue by laminectomy are justified. Intrathecal azoles have also been used.

Pseudoallescheria boydii infection. Allescheriosis or monosporiosis presents as a mycetoma. It is a rare cerebral mycosis which affects markedly compromised individuals.

The fungus *Allescheria boydii* belongs to the class Ascomycetes, which has a worldwide distribution and is a common soil saprophyte. The fungi are found in soil and water and present as septate hyphae. The organism has been isolated not only from sputum and pulmonary lesions but also in tissue from the lung. In most instances there has been an associated disease in the respiratory system, including sarcoidosis, chronic bronchitis, and emphysema. The organism gains access to the tissues through the skin (4).

When the organism infects the nervous system it may produce a meningoencephalitis with microabscesses in the brain.

In cerebrospinal fluid the organism appears as septated hyphae.

Neuropathology. This mycosis is only rarely the cause of meningitis or multiple brain abscesses. Mass lesions result from organisms producing hemorrhagic infarcts with associated leptomeningitis. These hemorrhagic infarcts may be converted into cerebral abscesses requiring surgical intervention. In brain tissue organism appear as septate hyphae. In the wall of the abscesses there are numerous hyphae and rounded clamydospores (38, 39).

Dapsone (diaminodiphenylsulphone) has been used in this mycosis.

Histoplasmosis. Histoplasmosis is present throughout the world and it is estimated that 25% of the population in the USA has contracted histoplasmosis; it is the most frequently observed pulmonary mycotic infection in the east and central United States (Ohio, Mississippi, and St. Lawrence river valleys); on the other hand its incidence in Europe is very low (6, 78). It is known to invade the reticuloendothelial system. Lesions are found in the spleen, liver, and lymph nodes, as well as in the lungs.

CNS involvement is rare, occurring in less than 1% of patients with active histoplasmosis. All ages and races and both sexes can be affected but there are two peaks of incidence: one in infancy and child-

hood involving the reticuloendothelial system and occasionally the meninges and the brain; the other in the fifth and sixth decades, during which period males are predominantly affected probably through reinfection; caseous nodules are found in various organs and there is involvement of the nervous system (25, 78).

The causative organism is *Histoplasma capsulatum*, a biphasic fungus that grows as a mycelial saprophyte in the soil but converts to a yeast-like organism in infected tissue. The organism is a budding yeast measuring 2-5μm in human tissue and in blood agar at 37°C. In preparations stained with H&E it appears much smaller because only its central part is visible, but it is well shown with PAS and silver impregnation. It is commonly found in soil. Organisms are inhaled with dust contaminated by chicken, bird, or bat excreta. The portal of entry is the lung where a primary focus is formed and commonly becomes calcified; however, primary lesions may occur in the mouth, gastrointestinal tract, or skin. A high proportion of individuals living in endemic areas have pulmonary lesions, but dissemination, especially to the CNS, is uncommon in immunocompetent individuals (6, 8). The presence of CNS disease implies impairment of the immune system by burns, antibiotics, steroids or other factors (39). Many patients with CNS involvement have AIDS (2, 85, 88, 89), although the incidence of histoplasmosis remain low in this risk group (9).

Clinically, the disease is characterized by splenomegaly, emaciation, irregular pyrexia, leukopenia, and anemia. Its onset in adult is insidious. After a few weeks of irregular pyrexia, patients may show a extreme nervousness and irritability, associated with a persistent cough. As the disease progresses there is a rapid loss of weight and a marked lethargy, leading to coma preceding death. Meningitis is proportionally less prominent in histoplasmosis than in cryptococcosis and coccidioidomycosis, and the available data do not permit conclusive statements about the pathogenesis. The occasional cases of histoplasmic meningitis are commonly associated with disseminated disease. Focal neurological findings are usually absent, although a tremor of the hands and a bilateral footdrop has been reported. The flat bones of the skull and the vertebrae may be affected and the latter may cause paraplegia by extradural spinal cord compression, and large paravertebral abscesses have been described (4).

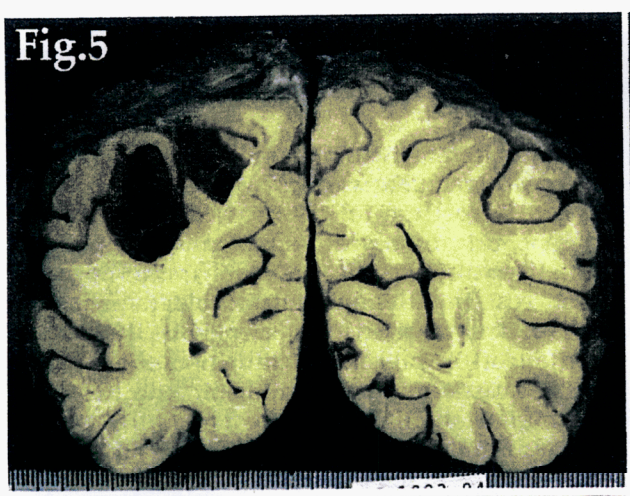
Neuropathology. In the nervous system, histoplasmosis usually causes diffuse or basilar leptomeningitis but may produce discrete intraparenchymal granulomas. There is thickening of the leptomeninges especially around the base of the brain. When the meningeal reaction is severe, it consists of thick yellow exudate with small scattered white nodules (miliary granulomas) along the blood vessels, and focal destructive lesions. These may be observed in the ependyma, and choroid plexus. In chronic cases there is meningeal fibrosis. A solitary intraparenchymal granuloma (histoplasmoma) may occur (6, 78).

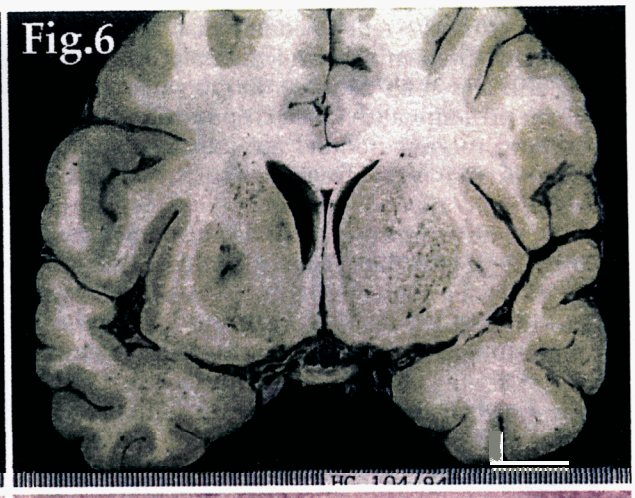
Histoplasmosis mimics in every aspect other infectious granulomas of mycobacterial and fungal origin. A spectrum of lesions is observed varying from nodular histiocytic formations with few organisms, to epithelioid cells ("tubercles") with Langhans' giant cells, the latter indistinguishable from tuberculosis or, if not caseated, from sarcoidosis. The demonstration of organisms in epitheliod-cell tubercles without caseation may be difficult, and the use of appropriate staining methods is essential for the diagnosis. Plasma cells and lymphocytes are found in the meninges, and granulomatous arteritis, similar to that seen in tuberculous meningitis, occurs either focally or in diffuse form. Necrosis of part or all of the arterial wall, with a variety of cell infiltrates, has been observed. Mass lesions in the brain consist of central caseous areas surrounded by macrophages, lymphocytes, plasma cells and giant cells. Organisms can be found within the cytoplasm of macrophages. In sections stained with H&E, shrinkage of the organisms produces a halo and imparts the spurious appearance of a capsule. Methenamine silver is especially useful to demonstrate the large numbers of organisms packed within macrophages. Adjacent reactive gliosis and fibrosis are present (39, 66, 79, 89).

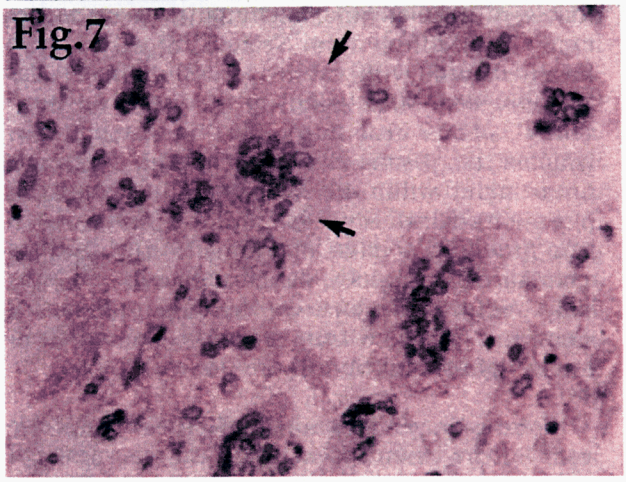
There is as yet no known effective therapeutic agent for the treatment of histoplasmosis, although sulphonamides, arsenical and antimony compounds and amphotericin B, combined with sulphonamides appear promising.

Cryptococcosis. Cryptococcosis, is a deep, visceral, systemic, or generalized mycosis which has been reported from almost all countries of the world and is the most frequent systemic mycosis found in humans in Europe. The disease affects individuals of all races, predominantly males (44); although this can be partly explained by greater outdoor exposure, there is also evidence that estrogens inhibit the growth of *Cryptococcus* (58). Sometimes it develops spontaneously in previously healthy people (57); however, in up to 85% of cases it is associated with debilitating illnesses (14, 29). Infection from person to person apparently does not occur, for reasons not at all clear. There are no remarkable differences related to occupation, with the exception of pigeon breeders, who, as it may be expected, are at special risk. The disease is more frequent in the fourth to the sixth decade of life. However, an increasing number of cases are reported in children up to 15 years of age (4).

The causative agent, *Cryptococcus neoformans*, is a spherical budding yeast which measures from 5 to 20 μm and is found in soil and wood that has been contaminated with bird excreta. It was originally referred







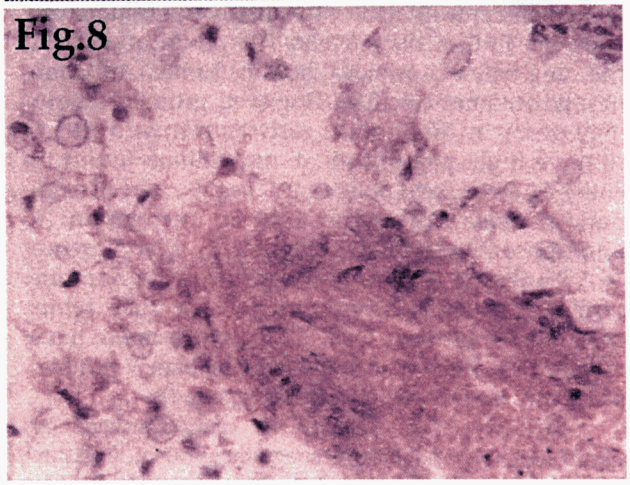


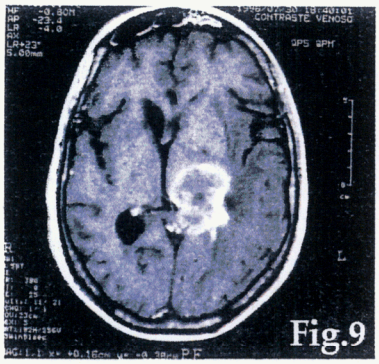
Figure 5. Cryptococcosis. Thickened opacified leptomeninges and two intraparenchymal cysts filled with gelatinous material.
Figure 6. Cryptococcosis. Multiple small cysts in the basal ganglia.
Figure 7. Cryptococcosis. Faintly stained cryptococci in the cytoplasm of multinucleated giant cells (arrows). H&E x 100 (on slide).
Figure 8. Cryptococcosis. Perivascular space containing numerous faintly basophilic cryptococci. H&E x 100 (on slide).

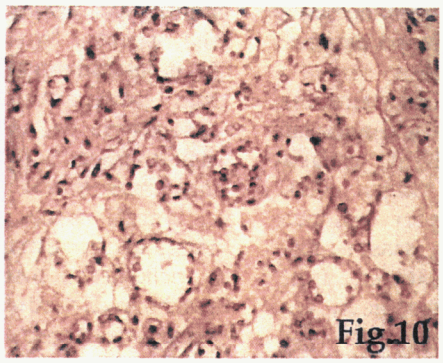
to as *Torula histolytica*. The fungus has been isolated from juices of various fruits and from milk. It is usually a single budding organism. Its main characteristic is a thick, mucinous capsule, a pattern unique in pathogenic fungi although not present in all strains of the organism. It grows rapidly in current culture media at room temperature and at 37°C (8, 39).

More than 50% of the patients in whom disseminated disease develops are immunocompromised. Predisposing conditions include lymphoproliferative diseases, alcoholism, age, generalized malnutrition, corticosteroid therapy, organ transplantation, collagen vascular diseases and, in recent years, AIDS (12, 17, 18, 21). On the other hand, patients with cryptococcomas are rarely in an immunocompromised state. Indeed, in these patients cryptococcosis appears to be the commonest mycosis (9, 40, 67). Patients with AIDS (>98%) or who are immunocompromised for other reasons (96%) are almost exclusively infected with *C. neoformans* variety *neoformans*, while *C. neoformans* variety *gattii* has a propensity for causing disease in immunocompetent hosts, suggesting that genetic and phenotypic differences are responsible for the different severity of the disease (44, 57, 74).

The portal of entry is certainly the respiratory tract, from which hematogenous spread occurs. However, a focus in the lungs may not be apparent or may have disappeared long before the manifestation of the cerebral lesion (62). Although all organs and tissues can be involved, there is a strong neurotropic tendency, with foci in the brain and especially in the meninges.

Nitric oxide (NO) and its derivatives have been shown to be important mediators of antifungal activity by murine macrophages and to inhibit directly *C. Neoformans* in vitro. IL-1β produced by microglia cells and IFN-γ a T cell cytokine provide signals for nitrite production by astrocytes (42) and it has been demonstrated that activated astrocytes can inhibit its growth in vitro probably by a NO-mediated mechanism (43). Cryptococcal meningoencephalitis in





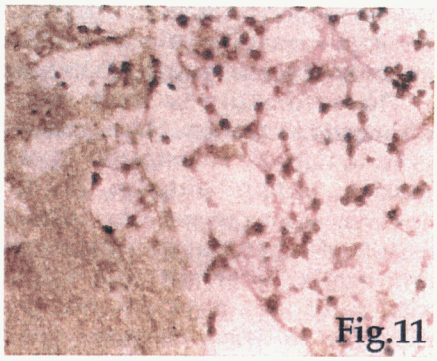


Figure 9. Cryptococcosis. NMR showing a large intracerebral cryptococcoma. Courtesy of Dr. CG Carlotti Jr.

Figure 10. Cryptococcosis. Fibrotic septa of a cryptococcoma enclosing numerous PAS positive cryptococci. HE x 62 (on slide).

Figure 11. Cryptococcosis. Leptomeningeal cryptococci stained with mucicarmine. Note the absence of inflammatory cells. x 65 (on slide).

patients with AIDS often involves the accumulation of yeast in brain with little inflammation or glial activation (20).

C. neoformans is unusual among fungal pathogens in that it has a polysaccharide capsule which is important for virulence (31). The capsule inhibits phagocytosis and impairs antigen presentation. Polysaccharide antigen is released during infection (20) and is a potential immunomodulator which has been reported to inhibit leukocyte migration (19), elicit suppressor responses (53), produce antibody unresponsiveness (31) and enhance infection of T cells by HIV *in vitro* (68). In cryptococcal meningoencephalitis, capsular polysaccharide dissociates from the fungal organisms resulting in the formation of tissue deposits and, given its major virulence factor and modulator of immune functions, it is likely to affect the interactions between the fungus and the nervous system/immune effector cells, thus contributing to the pathogenesis of the meningoencephalitis (41).

The symptomatology varies with the type and extent of the pathologic changes. The patient usually does not present the picture of an acute infection.

The predominant clinical features are almost always secondary to invasion of the CNS usually in the form of basal meningitis. The meningitis may be subacute or chronic and may lead to hydrocephalus. Cranial nerve disturbances occur irregularly. Papilledema, amblyopia, strabismus, diplopia, ptosis, and deafness have been reported. Gross focal manifestations such as hemiparesis exist at times (4).

The course of the disease is unpredictable. As a rule, it has a steadily progressive course over a period ranging from a few weeks to 6 months but occasionally extending from a year or longer. Periods of remission and relapse are common in untreated cases. Infections of rapid and fatal evolution with cryptococcal meningitis which terminate fatally within a few weeks are rare. In patients with localized granulomatous lesions (cryptococcomas), the duration of the neurological symptoms varies from 1 week to 6 years, and there are cases in which no neurological symptoms were observed throughout their lives (4).

The CSF is usually under increased pressure, usually clear, and rarely xanthochromic. The cell count may range from normal up to 1000 cells/cu mm, chiefly lymphocytes, but polymorphs may also be seen. The sugar and chloride levels may be reduced. The total protein content varies from almost normal to more than 500 mg/dl. Cryptococci are often identifiable on direct examination of the fluid, as yeast like cells. Examination of the CSF with "India ink" preparations is diagnostic in about 50% of cases, and can demonstrate the mucoid capsule (66).

Neuropathology. Grossly, CNS lesions may be minimal and can be overlooked. However, in most of the cases the leptomeninges are thickened and opaque. The exudate may occur at any site but is most often found over the base of the brain and cerebellum. Rare cases of spinal arachnoiditis have been reported. Some cases contain large amounts of organisms giving the surface of the specimen a mucinous appearance. On occasion, there may be formation of tubercles, 2-3 mm in diameter, adjacent to the blood vessels; their similarities to tuberculous lesions have been stressed (78). Meningitis may be subacute or chronic and may lead to hydrocephalus, chiefly in cases of longer survival due to chronic fibrosing leptomeningitis. About 50% of cases of CNS cryptococcosis show meningeal involvement exclusively. Less commonly, it produces multiple intraparenchymal cysts (Fig. 5) related to exuberant capsular material produced by the proliferating cryptococci and looking like soap bubbles, especially in the basal ganglia (Fig. 6). In rare cases masses of fungi aggregate in an inflammatory lesion and produce large or small granulomas (cryptococcomas or torulomas) in the meninges, parenchyma, ependymal surfaces, or choroid plexuses (6).

Histologically, the tissue reactions vary. In the cerebral lesions it may be of three types: a granulomatous meningitis, small granulomas or cysts within the cerebral cortex, and deep placed solid or cystic

nodules found chiefly in the grey matter of the basal nuclei. In some cases, it may be difficult to diagnose unless the organism is specifically sought.

The meningitis in most cases has minimal inflammatory reaction. The capsule of the organism seems to impede inflammation, possibly by partially masking surface antigens of the fungus (39). However, when present, the inflammatory response consists of collections of lymphocytes, plasma cells, eosinophils, fibroblasts and multinucleated giant cells. In the last, nuclei are often located more centrally than in typical Langhans-type cells, and cryptococci are frequently seen within them (Fig.7). In patients with AIDS, inflammatory and glial reaction is usually minimal. Adjacent neuroparenchymal lesions may be seen with the leptomeningitis.

In the gelatinous lesions, the solid tissue is replaced by numerous organisms forming a colony, usually around a vessel (Fig.8). The gelatinous aspect is due to the mucinous capsular material of the numerous organisms found invading the tissue. While no membrane or capsule surrounds these foci, they are nevertheless often sharply delineated from the surrounding tissue. Often there is little or no surrounding inflammatory reaction and gliosis. When present, cellular response consist principally of macrophages and scattered leukocytes, with occasional giant cells.

Granulomata are rare late reactions that can mimic tubercles and may appear on MRI as large masses (Fig 9). Histologically the nodules are composed of fibroblasts, giant cells, aggregates of organisms (Fig. 10) and include areas of necrosis. The organisms in these individuals are found within multinucleated giant cells and possess minimal capsule.

The organisms are faintly stained with H&E. The cell walls are strongly stained with the PAS, mucicarmine (Fig.11), Alcian blue and methenamine silver stains. When stained with picro-sirius and examined at polarized light they present themselves as bright yellow or red rings (3). The pathologist should be warned, however, that *C. neoformans* has staining reactions similar to those of corpora amylacea.

The drug of choice clearly appears to be amphotericin B, given intravenously. Flucytosine has also been reported to give good results.

Chromoblastomycosis. Chromoblastomycosis is a chronic cutaneous mycosis, involving predominantly a lower extremity. It is usually seen in adults, much more frequent in men than in women, and only exceptionally in children. There is no racial predilection. Most patients are field and forest workers. The disease has been reported from all the continents, but most cases have been seen in the tropical regions of America and Africa (4, 78).

It is caused by many different pigmented fungi including the genera *Cladosporidium, Hormodendrum* and *Phialophora.* All produce similar lesions in the human skin; therefore, it is not possible to identify the species by their appearance in tissues. *Cladosporidiun tricoides (bantianum)* is the organism most frequently isolated from the brain. Fungi are saprophytes in soil and decaying vegetation, and usually affect barefoot workers. They have been isolated from several organs including skin, conjunctiva, lymph nodes, oropharynx, upper respiratory, intestinal and urinary tracts and brain (78). Although *C. trichoides* is considered to be a pathogen, cases have been described in association with immunosuppressive treatment (60, 77, 83).

These organisms cause skin infections, appearing as verrucous, black-brown pigmented lesions. The basic lesion is a warty, discrete, firm nodule. It may be single or multiple, sometimes coalescing to give the appearance of a "mossy" skin. Cerebral chromoblastomycosis arises from an infected site outside the CNS that spreads to the brain via the blood stream (39). Cladosporiosis, the most frequent mycosis of this group, is nevertheless a rare disease (77).

The usual manifestation of brain involvement is abscess formation with or without meningitis (15, 52). Headache, coma and localizing neurological signs are associated with fever and a mass effect. Alternatively, meningitis may be the only manifestation (7). As for other mycoses, the CNS may be the only site of infection (77).

Neuropathology. The frontal lobe is the most commonly involved, but lesions in other lobes and in the cerebellum have also been described. Typically, single or multiple abscesses in the brain may enlarge to produce leptomeningitis or ventriculitis. The characteristic brown colour of the mycelium can be recognized macroscopically (15, 52, 77, 78).

Histologically, lesions are primarily intraparenchymal abscesses. They are larger than the microabscesses caused by the pseudohyphae of *Candida spp.* Granulomatous response may be minimal. Sometimes they contain the fungus and consist of lymphocytes, polymorphs, histiocytes and giant cells, and may be surrounded by fibrosis and reactive gliosis (78). Hyphae of these fungi are slender, from 2 to 3 μm in thickness, with indentations occurring at every 3-15μm interval. Branching may be present. They produce spores, and both these and hyphae are pigmented in culture and in tissues; however, because the pigment may not be apparent in stained sections with PAS and methenamine silver, unstained preparations should also be examined (39).

Unfortunately, there is not, to date, a satisfactory drug to treat this mycosis.

Sporotrichosis. Sporotrichosis is a chronic, usually benign, infection, that commonly involves muscle-skeletal tissues, mucous membranes, and viscera. The geographic distribution appears to have changed from the beginning of the century, and in more recent times, the disease has been most common in Central and South America, with the greatest preva-

lence in Brazil, although a small number of cases are still being seen in the United States, South Africa, and Japan. The disease has almost disappeared from the European countries (4, 8).

Sporotrichosis is caused by *Sporotrichum schenkii*, which is found in soil and on plants (6). Within tissues, *Sporotrichum* appears as a gram-positive, cigar-shaped body with occasional budding (8). In culture, the delicate, branching septate hyphae bear conidia laterally or in groups. The conidia are ovoid to spherical and are 2 to 6 µm in size.

As the fungus responsible is primarily a saprophyte growing on vegetation and in soil, it is understandable that occupations that involve close contact with these infected materials would predispose to infection.

Sporotrichosis may involve any of the tissues or organs of the body. Usually these lesions result from hematogenous dissemination, but in a significant number of cases the primary lesion cannot be found. In some instances, the infection may be introduced through the gastrointestinal tract. Pulmonary lesions may be the result of inhalation of spores.

This fungus generally produces skin infection by direct percutaneous inoculation. The initial lesions appearing at the site of entry of the fungus are, with few exceptions, through the dermis. In multiple ulcerating gummatous sporotrichosis the lesions start as subcutaneous gummas but ulcerate spontaneously within two to three weeks or after several months (4).

Rare cases of chronic meningitis and cerebritis have been reported (80). Meningitis presents as a chronic occipital headache and dizziness. Cerebral involvement results in transient episodes of aphasia, weakness, and visual disturbance which can terminate in complete paralysis, lethargy, and coma. Paraplegia, quadriplegia, and radicular pain occurs when the spinal cord is involved. The CSF shows pleocytosis, mostly lymphocytes, of up to 300 cells/cu mm, moderately increased protein level and reduced sugar level (4).

Neuropathology. In the cerebral form of the disease, the fungus may produce microabscesses, localized granulomas, or chronic meningitis.

Histologic lesions vary from a granulomatous basal meningitis to granulomatous microabscesses scattered throughout the cerebral cortex or involving the spinal cord rootlets. In tissue the fungus appears as small budding round or oval yeasts with short hyphae.

Deep mycoses are treated with amphotericin B, although the response does not appear to be good. 5-fluorocytosine can be added to the former.

North American Blastomycosis. Blastomycosis is an uncommon mycotic infection, that rarely involves the CNS. This disease exists predominantly in North America, is endemic in the south-eastern regions of the USA, but has also been reported widely in Africa. Even in endemic areas, however, its incidence is low. The lack of neurotropism, compared with that of cryptococcosis, is probably related to the fact that individuals with a normal immune system can mount a successful defense against this organism (6, 78).

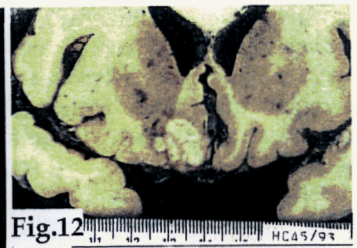
The causative agent, *Blastomyces dermatitidis*, is found in the soil and possibly in decaying wood in the eastern United States, and may have a natural reservoir in dogs. The fungus is a spherical cell, 8 µm to 15 µm in diameter, that multiplies by a single bud which is attached to the parent cell by a broad base. It affects predominantly adult males, mainly agricultural workers (6, 39). The fungus gains access to the body by way of the respiratory system and the lungs are the organs most commonly involved (59). The skin may also be a portal of entry, and the cutaneous form of the disease is limited to the face and exposed areas of the body. The CNS is involved in less than 5% of the cases (59), most often via the hematogenous route. Debilitating disorders and other predisposing conditions are not necessary for the establishment of blastomycosis in the CNS (39). Cerebral blastomycosis has rarely been encountered in patients with AIDS (28).

Blastomycosis may present clinically with a variety of signs and symptoms, most of them referable to the chest and lungs. Skin lesions are equally common, usually on the exposed surfaces of the body, as a subcutaneous nodule that gradually ulcerates and progresses to form verrucous, heaped up scaling lesions. Nonspecific signs and symptoms of an infectious disease may be pronounced or minimal.

CNS blastomycosis most often presents with headaches, neck stiffness. Intracranial blastomycotic abscesses or granulomas result in increased intracranial pressure with or without localized signs. Eventually, these patients develop convulsions, mental deterioration, confusion, and lethargy.(4)

The diagnosis may be made during examination of the CSF or by histologic evaluation of the granuloma (4, 39). The CSF may be clear or slightly turbid, and the pressure is usually increased. The cell count is slightly to moderately increased, seldom exceeding 500/cu mm, and either monocytes or polymorphonuclear leukocytes predominate. The total protein content is elevated, and sugar and chloride values are reduced. *Blastomyces dermatitides* may be present.

Neuropathology. Involvement of the nervous system may be expressed as meningitis, meningoencephalitis, brain abscesses, and dural abscesses. In various autopsy series, involvement ranges from 6 to 33%.Typically, cerebral blastomycosis produces leptomeningitis and adjacent granulomata (73). The lesion may be diffuse or localized to the base of the brain overlying an abscess and consists of a fibrinopurulent exudate which may cause obstructive hydrocephalus and/or become adherent to the dura.



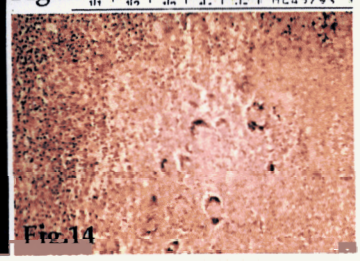


Figure 12. Paracoccidioidomycosis. Two chronic abscesses may be seen, one at the base of the left temporal lobe, the other, smaller, in the right temporal cortex.

Figure 13. Paracoccidioidomycosis. Sagittal section of high cervical spinal cord showing a well circumscribed necrotic lesion.

Figure 14. Paracoccidioidomycosis. A granuloma with central necrosis (right). Numerous multinucleated giant cells and surrounding inflammation. HE x 56 (on slide).

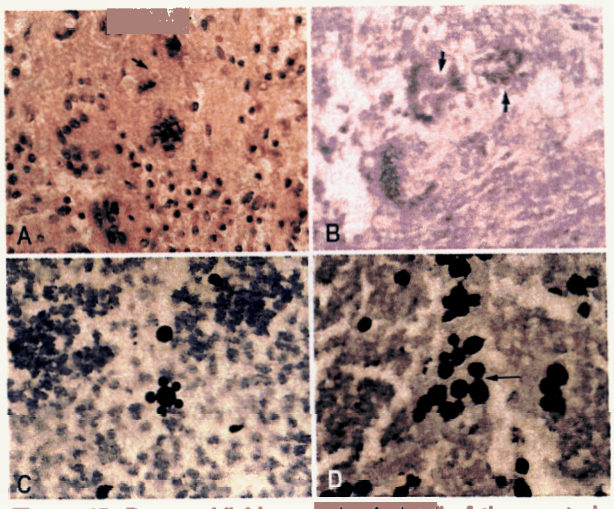


Figure 15. Paracoccidioidomycosis. A detail of the yeasts is shown at the arrows stained with (a) H&E x 180 (on slide) and (b) PAS x 180 (on slide). A smear preparation (c) and paraffin section (d) stained with methenamine silver. Multiple budding yeasts, some of them with a thin neck (d) - arrow. x 180 (on slide).

Fibrosis can occur in the subarachnoid space. The meninges may be involved from an extradural lesion that causes pachymeningitis leading to compression of the underlying brain or spinal cord. This condition may run a subacute or chronic course, and the prognosis is exceedingly poor. The infectious process may be associated with involvement of the bone. The cerebrum, cerebellum, basal ganglia, and spinal cord may be the site of single or multiple lesions. Overt abscess formation may occur, or the lesion may be hard and tumor-like (blastomycoma). Lesions in the pituitary have been described, as well as peripheral nerve involvement. On the other hand, lesions in the eye are rare (4, 78).

The histological reaction produced by *Blastomyces dermatitides* may vary from a purely supurative one to a fibrosing granulomatous process. *Blastomyces dermatitidis*, characteristically elicits a mixed granulomatous and suppurative reaction (6). The centre of an abscess contains caseous necrotic material, neutrophils and lymphocytes, and depending on the type of tissue reaction, it is surrounded by macrophages, lymphocytes and plasma cells, and epithelioid and multinucleated giant cells of the Langhans' type, some of which contain phagocytosed organisms (78). Tissue response varies according to the amount of organisms present. In tissues, fungi appear as singly budding yeast, 10-25 µm in diameter, with a broad neck and thick refractile cell walls. Careful observation can disclose the fungus in H&E and unstained wet preparations. Hyphae are not present. Special stains, such as PAS and methenamine silver, easily demonstrate the organisms. Long-standing lesions are enclosed within a thick capsule of hyaline connective tissue infiltrated with plasma cells (39, 78).

Amphotericin B the drug of choice in this mycosis.

Paracoccidioidomycosis. Paracoccidioidomycosis, or South American blastomycosis, is a chronic, progressive, and granulomatous disease, that mainly attacks the lungs, mucosa of the mouth and nose, and neighboring teguments, with frequent spread to the lymph nodes, adrenal glands, and other visceras. It was discovered in Brazil by Lutz (4), who observed lesions in the mucosa, and was able to culture the fungus. It is a disease of the New World, present from Mexico to Argentina (with the exceptions of Chile, El Salvador and Panama), and is the mycosis most frequently encountered in South American countries, especially Brazil, Venezuela and Colombia (4, 6, 8).

The infection is caused by *Paracoccidioides brasiliensis*. The causative organism has multiple thin-necked buds arising from a single yeast. The primary infection is in the lung (8). Rare cases of disseminate disease with multiple intracerebral granulomas have been attributed to this agent (55, 71). The organisms live in the soil or in vegetation. Plants could play a role as intermediate hosts for human infection. Such an assumption is based on the fact that there is a higher frequency of the disease among farmers and people living in rural areas. The fungus penetrates the oral, pharyngeal and nasal mucosa, producing different types of lesions, and then is carried to the lymph nodes, lungs, and other viscera by way of the lymph channels or the bloodstream. The oral mucosa is the favored portal of entry as inferred by the habit farmers have of using chips of wood or thorns as toothpicks and of chewing leaves or bark from trees. These objects can easily inflict wounds in

the mouth (4).

The anatomo-clinical manifestations of the disease have been classified as follows: tegumentary forms (mucocutaneous), lymphadenoid forms, visceral forms, and mixed forms. Pulmonary lesions are frequent and may be found in 84% of the patients.

Neurological manifestations of this deep mycosis are variable, depending on the involved site in the CNS. Meningitis may lead to obstructive hydrocephalus. Pseudotumorous forms in the brain or spinal cord may behave as space occupying lesions.

Neuropathology. Lesions in the CNS in paracoccidioidomycosis are infrequent. They are found principally in two forms, pseudotumor (71) (the so called blastomycoma or paracoccidioidomycoma) and the meningitic form. The former, which is the most frequent, manifests itself clinically as a space occupying lesion and anatomically as a necrotic nodule (fig. 12). These nodules are well circumscribed, similar to tuberculomas, of a size which varies from several millimeters to several centimeters, usually solitary (although there may be several), situated in the cerebral cortex or white matter. Similar lesions, although less frequent, can also occur in the spinal cord (fig. 13) (13). Leptomeningitis is a predominantly basal, granulomatous meningitis. These meningeal lesions spread to the brain through the Virchow-Robin spaces, especially at the level of the hypothalamus and the lateral fissures. Pseudotumors occur in the dura with clinical characteristics of meningiomas.

Granulomas are formed by epithelioid cells, Langhans' or foreign body giant cells or mixed with a lymphohistiocytic inflammatory infiltrate (Fig.14). The nodules may have a necrotic center, in which case they resemble a tuberculous lesion, unless the organisms are identified. Occasionally, the epithelioid nodules are not necrotic and giant cells are scanty. A chronic inflammation and fibrosis of the leptomeninges can also be observed. Routine H&E sections and special stains including PAS and methenamine silver demonstrate the organisms (Fig.15a-d), which appear in tissue as yeasts with round to oval bodies varying from 10 to 20 µm in diameter with single or multiple, attached thin-necked buds (39). Like *C. neoformans* they can also be demonstrated at polarized light as bright green rings when stained with picro-sirius (3).

Sulphonamides, alone or in combination with trimethoprim is used as well as amphotericin B and various imidazole compounds.

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