Modern treatment of the systemic fungus diseases

For many years the systemic fungus diseases received little attention from the members of the medical profession and in the curriculum of the medical schools in the United States. Recently there has been a gradual awakening to their importance. The introduction of increasing numbers of antifungal chemotherapeutic agents attest this new interest in the mycotic diseases. Beneficial or curative specific therapy is now possible for many of these diseases which previously were without effective means of treatment.

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The systemic fungus diseases are not common, and it is difficult to amass a significant number of patients with any one specific deep mycosis in order to evaluate clinically any new chemotherapeutic agent. This review has attempted to assemble and summarize the present-day knowledge of the newer antifungal agents. Individual consideration is given to the systemic fungus diseases: coccidioidomycosis, histoplasmosis, North American blastomycosis, South American blastomycosis, cryptococcosis, actinomycosis, nocardiosis, sporotrichosis, candidiasis, aspergillosis, and mucormycosis. Other contaminant fungi, such as species of Penicillium and Geotrichum, which at times assume a pathogenic role and cause disease, are not given individual consideration in this paper.

Since amphotericin B has given the most encouraging results of all the antifungal agents, greater attention is devoted to this antibiotic in this review.

Amphotericin B

Amphotericin B* is a polyene, antifungal antibiotic produced by a strain (M4574) of *Streptomyces nodosus* which was found in a soil sample obtained at Tembladora near the Orinoco River in Venezuela. It was first isolated and described by Gold, Stout, Pagano and Donovick[1] in 1955 and further characterized by others.[2-6]

Extraction of the whole culture broth in which the streptomycete is grown, or of the mycelial mat itself, yields a yellowish crude product containing amphotericin B, together with another active principle labeled amphotericin A. The extracting solvents used are water-saturated butanol; any of the lower alcohols, such as methanol, propanol, and, perferably, isopropanol; a water miscible solvent, like N,N-dimethylformamide or dimethyl sulfoxide. The two active principles may be separated from each other and purified by differential solution and precipitation. Further differentiation may

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be accomplished by specific optical rotation and ultraviolet absorption curves.

Physical and chemical properties.[1,4-7] Amphotericin B is a yellowish powder which is relatively insoluble. It is insoluble in anhydrous alcohols, acetone, ethers, chloroform, benzene, toluene, ethyl acetate, glacial acetic acid, pyridine, or alcoholic potassium hydroxide. It is soluble only to a small extent in water at pH 2 and pH 11. Solubilized preparations, however, in the form of colloidal dispersions suitable for biologic work, have been made possible with the use of sodium desoxycholate. A melting point cannot be determined as the compound darkens and decomposes gradually above 170°C. The specific optical rotation in 0.1 methyl hydroxide-hydrochloric acid $[a]_D^{23,5C}$ is −33.6 and in acid dimethylformamide $[a]_D^{23.5C}$, +333. Its ultraviolet absorption curve is characteristic of a conjugated heptaene, like ascosin or trichomycin. The curve of amphotericin A is that of a conjugated tetraene, like rimocidin or nystatin.

Amphotericin B is amphoteric. The neutralization equivalent when it is titrated as a base is 929. It gives a negative ferric chloride test and a positive Molisch test and decolorizes potassium permanganate or bromide-carbon tetrachloride. Elementary analysis shows carbon, hydrogen, and nitrogen, but not halogen, sulfur, methoxyl or acetyl groups. The empirical formula of $C_{46}H_{73}O_{20}$ has been tentatively assigned to it. Evidence indicates a basic moiety of aminodesoxyhexose, for which the name "mycosamine" has been proposed.

Assay methods.[1,6,8-11] With the increasing use of amphotericin B, bioassay methods to determine the amounts of the drug in biologic fluids have been described, utilizing essentially the tube serial dilution technique or the agar diffusion method. These methods have not been standardized as yet. The test organisms used are *Candida albicans, Histoplasma capsulatum,* and *Saccharomyces cerevisiae.* Growth inhibition is measured by visual turbidity readings, turbidimetric determinations with the spectrophotometer, or direct counts of the organisms in a hemocytometer chamber.

Absorption, distribution, and excretion. Amphotericin B is poorly absorbed through the gastrointestinal tract in mice,[12,13] in dogs,[14] and in man.[6,8,12] Only maximal values of 0.03 to 0.08 μg per milliliter plasma were obtained in dogs 18 hours after a single oral dose of 500 mg. of amphotericin B. None was detected in the heart, liver, or spleen. Only 0.1 per cent of the daily dose was excreted in the urine during a 5 hour period, and 65 to 87 per cent was recovered from the stools during one 24 hour period.[14] In 13 patients given oral amphotericin B, the blood levels found were low. The spinal fluid frequently showed none, or very small amounts, of the drug. Only small quantities appeared in the urine.[8]

Clinical experience has shown that in patients who did not respond to the oral, subcutaneous, or even intramuscular administration of amphotericin B, assayable serum levels of the drug with resultant favorable clinical response could be achieved by intravenous infusion.[6,8,10,15] The blood level dropped considerably during the first 24 hours after intravenous administration, then gradually thereafter. It was still possible to demonstrate serum levels a month later.[11] The spinal fluid level is low, being 1/30 to 1/50 of the serum levels. The excretion through the urine is small and slow.

Toxicity in animals.[3,16] In acute toxicity studies with intravenous solubilized amphotericin B, the estimated lowest lethal dose (LD_2) and mean lethal dose (LD_{50}) for mice were 1.8 and 2.3 mg. per kilogram of body weight and 4.0 and 4.3 mg. per kilogram of body weight, respectively. In chronic toxicity studies, no toxic evidence was observed in two groups of 50 mice each given amphotericin B intraperitoneally in daily doses of from 5 to 100 mg. per kilogram of body weight for 50 and 71 days, respectively.

Apparently there are species differences. In rabbits, 62 per cent of 19 animals died 10 to 30 minutes after intravenous administration of 5.0 to 6.6 mg. per kilogram of

body weight. Death was preceded by a rise in the blood urea nitrogen and by tremors and convulsions. In dogs, intravenous doses as low as 1.0 mg. per kilogram of body weight elicited an unusual and specific intestinal reaction, with anorexia, emesis, hematemesis, and bloody diarrhea. Autopsy showed hemorrhagic involvement of the duodenum primarily. Three of 4 monkeys given 2.0 mg. per kilogram of body weight per day intravenously 5 days a week for 3 to 4 weeks showed neither acute nor delayed toxicity, except for occasional vomiting, sclerosis of veins, and elevation of the blood urea nitrogen.[7]

Toxicity in man. Oral amphotericin B is relatively nontoxic and, except for occasional mild gastrointestinal upsets, it is well tolerated, even in relatively large doses. When given intravenously the drug is more toxic, with a maximal tolerated dose of 1.0 to 1.6 mg. per kilogram of body weight. The chief toxic effects encountered are fever, nausea, emesis, anorexia, and azotemia, with the appearance of cellular and granular casts in the urine, as well as hematuria and proteinuria. The renal toxicity produced by amphotericin B represents the most serious drawback to the use of this antibiotic. The rise in the blood urea nitrogen which may occur during intravenous therapy is temporary and, after 2 to 7 days' rest, normal values are obtained. The antibiotic therapy can then be safely continued. The other toxic manifestations can be partially controlled by the use of chlorpromazine in a dosage of 50 mg. administered prior to the amphotericin B therapy, and soluble hydrocortisone in a dosage of 20 mg. administered with the intravenous amphotericin B suspension. There is question as to the wisdom of administering steroid hormones to patients with granulomatous disease; however, there has not yet been evidence of undesirable effect. The intravenous solution of amphotericin B should be administered by slow drip, and adjusted so that a minimum of 6 hours is required for the full daily dose. Toxicity can be minimized by strict attention to this simple procedure. The drug is best tolerated if administered every other day, rather than on consecutive days.

Antifungal spectrum. The results of the early in vitro studies[1-3,12,13,17] indicating marked fungicidal action of amphotericin B against a wide variety of pathogenic fungi, especially the systemic species *Candida albicans, Cryptococcus neoformans, Blastomyces dermatitidis, Blastomyces brasiliensis, Sporotrichum schenckii,* and *Histoplasma capsulatum,* have been substantiated by favorable findings in laboratory animal infections,[3,12,13,18-20] and by an expanding clinical experience in the treatment of human infections due to these fungi. Amphotericin B has no significant antibacterial activity.

Dosage and administration. The most effective mode of administration is by intravenous infusion. The parenteral soluble preparation of the drug comes as a sterile, lyophilized powder in vials each containing 50 mg. of amphotericin B and 41 mg. of sodium desoxycholate with a sodium phosphate buffer. Inasmuch as saline solution causes precipitation of the antibiotic, the recommended solvent is 5 per cent dextrose in water. The optimum concentration is between 0.1 mg. and 0.5 mg. per milliliter solution.

The optimum adult dose is 50 mg. per day, although the drug should be initially given at a dose of 25 mg. per day and gradually increased, depending upon the reaction of the patient. If toxicity develops with daily administration, the drug may be given on alternate days, or even stopped temporarily and resumed at a lower dosage level. The treatment course usually runs from 20 to 60 days, but may be longer if the clinical response of the patient is not satisfactory within that period.

When especially indicated, amphotericin B may be administered orally (2 to 10 Gm. daily), intrathecally (up to 1 mg. every other day), intramuscularly, intra-articularly (up to 25 mg. every other day), as an aerosol intrapulmonary spray (5 mg. every 6 hours), intrathoracically (up to 3 mg.), or

into the cutaneous lesions (up to 25 mg. with 2 per cent procaine every other day).[21]

Coccidioidomycosis

Coccidioidomycosis is one of the most prevalent and important of the deep mycoses. It is caused by *Coccidioides immitis,* a fungus indigenous to the arid regions of the southwestern United States. The principal focus of coccidioidomycosis is localized to the San Joaquin Valley of California, with known endemic areas in Nevada, Arizona, New Mexico, Texas, and northern Mexico.[22] Although the disease is acquired only in these areas, it has become a problem to all physicians regardless of their geographic location, for travel ultimately takes a large percentage of the United States population into the endemic areas. The arthrospore phase of *Coccidioides immitis* has been isolated from soil specimens, especially those taken from the burrows of desert rodents. These animals may serve as the reservoir for this disease.[23,24] Once infection develops in the human, the arthrospore, or vegetative phase of *Coccidioides immitis,* changes to a spherule stage. The spherule, which is laden with endospores, is seen on microscopic examination of infected human tissue. The organisms, which are quite characteristic in their shape, are normally 20 to 80 μ in diameter.[25] These spherules grow quite readily on artificial agar, producing a fluffy, white to brownish-white aerial hyphal growth, which segments into closely jointed structures called arthrospores. Such cultures are highly infectious and must be handled with great care by laboratory personnel.[26] There has been no known instance of human-to-human transmission of this disease.

Except for the rare instance of primary cutaneous inoculation coccidioidomycosis, the disease is acquired by inhalation of the causative arthrospore. When cutaneous inoculation occurs, a primary ulcerative granuloma resembling primary inoculation tuberculosis develops at the site of the inoculation. Satellite lymphadenopathy then develops, and the disease has been reported to run a completely benign course without evidence of dissemination.[27] Following inhalation of the causative agent by a previously uninfected person, the disease is usually confined to a focal area of the lungs, producing such mild disease that 70 per cent of the cases remain subclinical and unrecognized.[22] When symptoms occur, they are those of upper respiratory infection, usually revealing on roentgenograms of the chest areas of patchy infiltration, nodular infiltration, and pneumonitis, along with occasional pleural effusion and hilar lymphadenopathy. This type of patient may develop allergic manifestations such as erythema nodosum, erythema multiforme, or urticarial eruptions. Total healing takes place within a matter of several weeks to several months. Approximately 5 per cent of patients who have severe primary pulmonary coccidioidomycosis will be left with residual manifestations, consisting of thin-walled pulmonary cavitation. A much smaller percentage, less than 0.5 per cent of white-skinned persons, will develop disseminated coccidioidomycosis following primary pulmonary inhalation.[22] The Negro and Filipino are much more susceptible to the development of disseminated coccidioidomycosis than is the Caucasian.[28] When dissemination occurs, the spherules are spread via the blood stream and lymphatics throughout the body. There is no organ system which is immune to the development of coccidioidomycosis.

Treatment. No discussion of the therapy of coccidioidomycosis would be complete without mention of the immunology of the disease. Smith[29,30] has demonstrated very conclusively that a rising complement fixing antibody titer very closely parallels dissemination of the organism. As the complement fixing antibody titer rises, it is probable that the coccidioidin skin test sensitivity will be lost.

Until amphotericin B became available in 1956, there was no effective chemotherapeutic means of treating disseminated coccidioidomycosis. Prior to that time, the aromatic diamidines had been given a more

than adequate trial.[31-34] They were not effective in producing the same clinical improvement found with their use in North American blastomycosis. It must be concluded that they have little or no value in the treatment of disseminated coccidioidomycosis. The antibiotic, nystatin,* shows in vitro inhibition of *Coccidioides immitis*.[35-37] This drug, when administered intravenously or intramuscularly, causes severe chills, fever, malaise, and emesis to such extent that it is no longer in use. The oral absorption of nystatin from the gastrointestinal tract is so poor that no clinical effect can be obtained by the administration of the drug via this route. The broad-spectrum antibiotics, oxytetracycline, chlortetracycline, tetracycline, penicillin, as well as the sulfonamides, have not shown any in vitro inhibitory effect on *Coccidioides immitis*.[38] The sex hormone, diethylstilbestrol, has been reported to show in vitro effect on *Coccidioides immitis;* however, no clinical response has been obtained from such therapy.[39] Consistently good results have also been lacking with testosterone, methyltestosterone, and testosterone propionate.[40] There was evidence that the antibiotic, protoanemonin, would be clinically effective; however, this has not been substantiated.[41] Sodium caprylate, ethyl vanillate, fradicin, thiolutin, and prodigiosin have been ineffective in the treatment of the systemic form of the disease.[42-44] Many other chemotherapeutic agents besides those mentioned have been tried in this systemic fungus disease. They have all been universally ineffective in controlling the spread of the causative agent, or preventing death from the disease.

Amphotericin B is the treatment of choice for coccidioidomycosis, when therapy is indicated. Indications for treatment include: (1) primary pulmonary coccidioidomycosis in the Negro or Filipino, (2) a residual pulmonary cavity, which is increasing in size and causing increasing hemoptysis, or which has ruptured with spontaneous pneumothorax or empyema, (3) rising complement fixing antibody titer well beyond the time of the primary pulmonary infection, (4) any clinical evidence of dissemination of the disease, (5) any type of surgical procedure, particularly corrective pulmonary surgery, (6) pregnancy, since this condition is associated with an increased risk of dissemination. The first case report of the use of amphotericin B in coccidioidomycosis was by Halde, Newcomer, Wright, and Sternberg.[12] This preliminary report recorded a failure from the use of the drug administered orally. The second report by Fiese[45] recorded a favorable response from large amounts of amphotericin B given orally. Klapper, Smith, and Conant[46] recorded an apparent cure with orally administered amphotericin B in amounts of 4 Gm. per day for 10 months, followed by 2 Gm. per day for an additional 4 months. Other authors[47,48] have reported failures following the use of amphotericin B given orally. It is apparent that the greatest effect from this drug is obtained when it is administered intravenously. Littman, Horowitz, and Swadey[6] have reported excellent results with the intravenous use of amphotericin B in 4 patients with disseminated coccidioidomycosis. Other authors[48,49] have also reported benefit from this antibiotic when given in adequate amounts intravenously. It is difficult to understand why the 3 patients with disseminated coccidioidomycosis discussed by Utz, Treger, McCullough, and Emmons[50] failed to show any response following an adequate intravenous course of this drug. It is not likely that these 3 patients had strains of *Coccidioides immitis* which had become resistant to amphotericin B. Such resistance has been artifically developed in vitro.[51] We have had the occasion to treat one patient with coccidioidomycosis with intravenous amphotericin B. In April, 1957, a 28-year-old white male U.S. Army veteran was seen at the University Medical Center in Ann Arbor, Michigan, for an isolated cavity of the right upper lung. The patient related that he had been aware of the cavity for the 5 years following his discharge from the U.S. Armed Forces. He had been stationed in the San

*Mycostatin, E. R. Squibb & Sons.

Joaquin Valley during part of his time in the United States Army. One unsuccessful attempt at surgical removal of the cavity had been performed elsewhere before the patient was seen by us. The case was interpreted as one of a solitary, thin-walled cavity as the sole remaining evidence of previous primary pulmonary coccidioidomycosis. No evidence of dissemination was present. *Coccidioides immitis* was readily found on examination of the patient's sputum, and positive cultures were obtained on Sabouraud's glucose agar. The patient's chief complaint was that of increasing hemoptysis. He did not desire further surgery. He was treated with amphotericin B, administered in a daily dosage of 50 mg. dissolved in 1,000 c.c. of 5 per cent glucose in water given by slow intravenous drip on consecutive days for 20 days. He received a total dose of 1.0 Gm. of amphotericin B. By the time the patient had received the sixth injection of amphotericin B, his sputum became mycologically negative, and all evidence of hemoptysis ceased. He ceased to raise sputum altogether by the time the course of 1.0 Gm. of the drug had been given. He developed a mild febrile response and nausea with each intravenous injection. Prior to the institution of amphotericin B therapy, the cavity measured 3 cm. in diameter by x-ray examination. One year following the amphotericin B therapy, the patient had remained completely asymptomatic. There was still x-ray evidence of pulmonary cavity; however, it had decreased in size to approximately 1 cm. in diameter. He has since been lost from our observation. This patient had a negative coccidioidin skin test, and his serum was negative for complement fixing antibodies.

Although a very limited number of patients have been reported to be treated with amphotericin B via the intravenous route, there is good evidence that this rather toxic antibiotic has a profound in vivo antifungal effect. The optimum total dose of amphotericin B remains to be determined.

Surgical excision of an isolated pulmonary cavity should be considered if the cavity cannot be closed by amphotericin B therapy or by pneumothorax or pneumoperitoneum. Complications accompanying pulmonary operation for coccidioidal cavities have been few, but relatively serious. Any surgical procedure performed on a patient with coccidioidomycosis should be accompanied by amphotericin B therapy.

Histoplasmosis

Numerous epidemiologic studies and histoplasmin skin test surveys have radically changed the old concept of histoplasmosis as being a rare and fatal disease. It is now known on all continents, with the highest reported endemicity in the East Central states of the United States bordering the tributaries of the Ohio, Missouri, and Mississippi rivers.[52,53] In these endemic areas, the incidence of histoplasmin reactors may reach the figures of 80 to 90 per cent of the population.

The disease is caused by *Histoplasma capsulatum,* which is dimorphic like *Blastomyces dermatitidis, Blastomyces brasiliensis,* and *Sporotrichum schenckii.* The tissue forms are small, 1 to 5 μ in size, round or oval, yeastlike budding organisms, predominantly located in reticuloendothelial cells. The saprophytic phase is mycelial, producing characteristic tuberculate chlamydospores which are considered as the infective structure of the organism in natural exposures. The reservoir in nature is the soil, as indicated by repeated isolation of the organism from soil samples—particularly those associated with chicken and bat droppings from endemic areas and from point sources of reported epidemics.[54] Evidence points to histoplasmosis as being an airborne infection, with the respiratory tract as the major portal of entry. Under normal conditions of exposure the infection may be so mild as to be asymptomatic; or, if symptomatic, after an incubation period of 5 to 15 days, it may appear as an influenza-like or respiratory condition, usually mistaken for a common cold, tuberculosis, bronchopneumonia, or other nonmycotic

ailments. The x-ray findings are hilar adenopathy and/or parenchymal infiltrates. Precipitins and complement fixing antibodies appear, and the histoplasmin skin test becomes positive. As a rule, the patient recovers after a few weeks, although the pulmonary lesions may persist and eventually become calcified. Not more than 1 per cent of the primary infections progress to the disseminated, fatal form, although recently more and more cases of the chronic progressive pulmonary type of histoplasmosis (which closely resembles chronic fibrocaseous pulmonary tuberculosis) are being recognized, particularly in tuberculosis sanatoria.[55] The disseminated form with fever, weakness, anemia, wasting, and hepatosplenomegaly is the classical clinical picture by which histoplasmosis was previously known.

Histoplasmosis is generally regarded as a protean disease running the gamut of symptomatology from a mild, almost subclinical upper respiratory infection to an overwhelming, fatal septicemia, with the clinical picture related to the sites involved. Furcolow[56] described the following clinical types:

1. Severe
   a. chronic progressive (reinfection or cavitary)
   b. acute progressive
   c. acute epidemic
2. Moderately severe
3. Mild
4. Asymptomatic

The significance of immunologic phenomena in histoplasmosis parallels that in coccidioidomycosis and North American blastomycosis.[57] Precipitins and complement fixing antibodies become measurable during the early stage of the infection. They disappear as the illness subsides, thus indicating the severity and extent of the disease process. The skin hypersensitivity, as demonstrated by the histoplasmin skin test, develops from 4 to 6 weeks after the onset of the disease and persists for many years. Its significance is similar to that of the tuberculin test, indicating a past or present infection. It may be used as a measure of resistance of the body to the infection. The complement fixation test and the histoplasmin skin test are interpreted together for diagnostic and prognostic purposes and are valuable tools in the evaluation of the effectiveness of the treatment instituted.

Treatment. The extreme variation in the clinical picture and course of histoplasmosis makes the evaluation of therapeutic modalities difficult. Immunologic mechanisms apparently play a significant role and should be considered in the response of the patient to therapy, which varies markedly depending upon the severity and clinical type of the infection. This becomes important in the absence of an effective etiological treatment.

The acute primary pulmonary infection is generally benign and self-limited, thus nonspecific supportive and symptomatic measures suffice. Many patients do not even seek medical assistance. However, this type of case may occasionally become severe enough to threaten the life of the patient as may occur in the acute epidemic form with unduly massive exposure to the infective organism.[58] The question of the use of steroids in these cases has been raised in spite of their known association with dangerous spread of infectious processes. Although Baum, Adriano, and Schwarz[59] failed to observe any influence of cortisone on the dissemination of experimental histoplasmosis, others[60-62] obtained evidence of wider spread. In clinical trials, certain authors noted an association of the spread of the infection with administration of steroids,[63-65] while others thought that the steroids contributed to the clinical improvement and the clearing of lesions.[66-68] A special indication for the use of steroids in histoplasmosis has been pointed out by Schwartz[69] and Packard, Finkelstein, and Turner.[70] Carefully controlled administration of steroids may even prove lifesaving by virtue of their anti-inflammatory and antitoxemic effects in patients threatened by a self-limited but massive acute pulmonary infection with severe toxemia and high fever.

The drugs, however, should not be given during the first 2 weeks of illness when the body has not yet had the chance to build up adequate immunologic defense. The risk of dissemination may be minimized by the concomitant administration of one of the more successful histoplasmostatic agents as was done by Tegeris and Smith,[68] who used cortisone and MRD-112. The use of amphotericin B as an antifungal "cover" may be more promising.

The problems encountered in the management of chronic pulmonary histoplasmosis are similar to those in chronic pulmonary tuberculosis.[55] The indications for sanatorial treatment, supportive and symptomatic measures, and surgical intervention are similar, except for the lack of an accepted specific drug in histoplasmosis. Surgical excision of localized lesions has proved of definite value.[71-74]

The almost uniformly fatal course of progressive disseminated histoplasmosis highlights the need for an effective specific drug. The newer drugs that have shown a certain measure of success are ethyl vanillate, β-diethylaminoethyl fencholate (MRD-112), and sulfadiazine, but they are being discarded in favor of the more effective amphotericin B. The aromatic diamidines and nystatin are generally considered ineffectual in clinical trials.

Ethyl vanillate (ethyl-4-hydroxy-3-methoxybenzoate) was first used clinically in 1951 by Christie, Middleton, Peterson, and McVickar[75] on 12 children with disseminated histoplasmosis. Five recovered. Subsequent trials by other authors[76-84] gave variable results. The drug is administered orally in large doses up to 40 Gm. It causes distressing gastrointestinal irritation and serious toxic reactions, with a narrow margin of safety between the toxic and the therapeutic doses. These are distinct disadvantages, especially with the introduction of other drugs, equally effective but less toxic.

Ludwig, Murray, Smith, Thompson, and Werner[85] demonstrated the in vitro antifungal activity of MRD-112 at a concentration of 0.1 mg. per milliliter of medium. As with ethyl vanillate, the therapeutic results in humans with the use of MRD-112 have been inconsistent.[66,84,86-91] The drug is given for 1 to 2 months in daily doses of 150 to 600 mg. as a slow intravenous drip. Except for some evidence of hepatic degeneration, it has not shown serious toxicity.

The results of laboratory studies on the in vitro and in vivo antifungal activity of the sulfonamides on *Histoplasma capsulatum* have been contradictory, although the recent reports of Mayer, Eisman, Geftic, Konopka, and Tanzola[92] and Louria and Feder[93] agreed on their effectiveness in protecting mice against experimental histoplasmosis. The clinical use of sulfonamides in human histoplasmosis has generally been regarded as disappointing. There are, however, reports of favorable results, and, recently, Christie[94] has reinvestigated the problem by treating 3 cases of progressive disseminated histoplasmosis and 2 cases of the ulceroglandular type with sulfonamides. All five achieved clinical remission. It is to be noted that Latin-American authors have taken exception to the general opinion that sulfonamides are ineffective in histoplasmosis. Their successful experience in improving the prognosis of South American blastomycosis with the use of sulfonamides has led to their use of these drugs in cases of histoplasmosis, resulting in more satisfactory clinical responses and a number of apparent clinical cures through the administration of large doses for prolonged periods.[95-101] Cordero[98] felt that most of the reported clinical failures were due to relatively small doses or short periods of administration. As in South American blastomycosis, the sulfonamide preparations, particularly sulfadiazine, are given orally in daily doses of 3 to 6 Gm. for months.

The best therapeutic results so far have been obtained with the use of amphotericin B. The number of cases reported is still relatively small, and the periods of post-treatment observation still too short for exact evaluation of its value; but the preliminary findings are certainly promising.

The inhibitory in vitro concentration of the drug against *Histoplasma capsulatum* is very low, as little as 0.04 μg per milliliter of medium.[1,3,13,102] The drug is highly protective in experimental histoplasmosis in animals.[2,19,20,103] Amphotericin B has been tried on at least 34 cases of human histoplasmosis.[11,16,20,50,91,104-110] Two patients with acute pulmonary histoplasmosis improved. Although the fall in temperature and the rapid resolution of the infiltrates coincided with the institution of therapy with amphotericin B, the claim of improvement is at most suggestive in view of the good prognosis of this form of histoplasmosis. Nine cases of the chronic pulmonary type were treated. The symptoms were arrested in one, improved in 7, and no change appeared in one case with oral administration of 2.0 to 4.0 Gm. of the drug daily for 40 days. Eighteen cases of progressive disseminated histoplasmosis were treated. Seven clinical remissions were observed, with follow-up periods ranging up to 18 months. Nine patients improved dramatically. One also showed improvement with oral treatment, but died in 7 months. Three other deaths occurred, but the drug was administered only a few times during the terminal stages of the disease. Certainly these figures are unparalleled.

North American blastomycosis

North American blostomycosis is caused by the fungus, *Blastomyces dermatitidis*, an organism which grows readily on Sabouraud's glucose agar at room temperature as a filamentous mold, and on blood agar at 37° C. as a yeastlike fungus. The tissue phase of the fungus appears as a characteristic single-budding structure of 5 to 15 μ in diameter, and exhibits a refractile cell wall from which the protoplasm has often shrunk away, giving a double-contoured appearance. The polysaccharide wall of the organism is well demonstrated in tissue by means of the periodic acid–Schiff stain. The diagnosis of North American blastomycosis can be established by cultures or by the finding of the causative agent on direct microscopic examination of pus obtained from the cutaneous lesions or from other infected clinical material.

North American blastomycosis is most frequently encountered in the Southern, Southeastern, and Midwestern areas of the United States. Cases of the disease have been reported sporadically from other geographic areas of the United States as well as Canada.[111] There is doubt that the disease has been acquired outside of the North American continent, even though case reports from other continents are in the medical literature. *Blastomyces dermatitidis* has not, as yet, been isolated from the soil in which it must logically exist.[112] The organism shows a decided tendency to produce disease in the male sex. Reported ratios of men to women average approximately ten to one.[113-115] The disease has now been reported in siblings[112] and develops in all age groups. One small epidemic of North American blastomycosis has recently been reported.[112]

North American blastomycosis is nearly always acquired by inhalation of the causative fungus. This somewhat revolutionary thought was first advanced by Schwarz and Baum,[116] and it has been slow to be generally accepted. The rare person who has had known primary cutaneous inoculation blastomycosis has followed a clinical pattern resembling that of primary inoculation tuberculosis or sporotrichosis.[117,118] There has been no instance recorded of known primary inoculation blastomycosis developing into a systemic blastomycosis. There is now evidence that a subclinical form of pulmonary blastomycosis occurs, similar to that encountered in coccidioidomycosis and histoplasmosis.[112,113,115] The blastomycetes are disseminated from the lungs via the blood stream and lymphatics to other organs of the body, with a predilection for the skin, subcutaneous tissue, and bone. Pulmonary blastomycosis mimics most of the other deep mycoses, as well as tuberculosis, while the cutaneous granulomas also closely simulate tuberculosis, tertiary syphilis, other deep mycoses, and certain drug eruptions.

Treatment. The therapy of North American blastomycosis should not be discussed without emphasis, first, upon the importance of correlating the results of therapy with the immunologic status of the patient. Smith[119] was the first to recognize that the prognosis of a patient with blastomycosis is dependent to a large extent upon the immunologic response of the individual. The prognosis is best in patients who have a positive blastomycin skin test and no demonstrable complement fixing serum antibodies. Spontaneous cure has been reported[112] in a patient who exhibited this immunologic pattern. The prognosis is poorest in those patients who have a negative blastomycin skin test and a high titer of complement fixing serum antibodies.

2-Hydroxystilbamidine and amphotericin B, both administered intravenously, represent the two present choices for chemotherapy of North American blastomycosis. Evidence is accumulating that amphotericin B will prove to be superior to 2-hydroxystilbamidine. The use of 2-hydroxystilbamidine in generalized North American blastomycosis was first reported by Snapper, Schneid, McVay, and Lieben.[120] This aromatic diamidine does not cause the toxic neurological effect which was almost universally recorded with stilbamidine when the latter drug was given in doses greater than 1 Gm.[120-125] Very excellent reviews have been reported on the aromatic diamidines.[120,126,127] 2-Hydroxystilbamidine has gained widespread acceptance in the therapy of North American blastomycosis.[38,115,128] This drug is supplied in vials of 225 mg. The dose of 450 mg. of the drug is as well tolerated as is the smaller 225 mg. dose. This amount of 2-hydroxystilbamidine is dissolved in 500 to 1,000 c.c. of 5 per cent dextrose solution or isotonic saline and administered intravenously by slow drip. The solution is made up each day, just prior to its administration. Care should be taken to keep the drug from direct sunlight, since it has been well documented that toxicity of the compound increases upon exposure to direct sunlight. The drug is administered on consecutive days, although rest periods of days to weeks may safely be given. A course of 9.0 Gm. of 2-hydroxystilbamidine represents an adequate course of the drug. Healing of the cutaneous lesions and symptomatic improvement are usually noted by the end of the second week of therapy. Complete healing has usually taken place by the end of the first month following the cessation of therapy. 2-Hydroxystilbamidine is deposited in various organs, especially the liver, kidneys, adrenals, sweat glands, and skin,[120,127] and continued improvement occurs for at least several weeks following the last administration of the drug.

There are reports documenting relapse of North American blastomycosis following adequate amounts of aromatic diamidine therapy.[129-131] Most of these recurrences have been in individuals who have contributed little to their own immunologic defense, as evidenced by negative blastomycin skin tests and positive complement fixing antibody tests. There is also evidence that resistance to 2-hydroxystilbamidine is developed by specific strains of *Blastomyces dermatitidis*.[132]

Intravenous amphotericin B therapy has proved effective in 8 cases of North American blastomycosis treated at the University of Michigan Medical Center.[118] Five of these successes occurred in patients who had exhibited repeated relapses following massive amounts of aromatic diamidine therapy.[118] Utz, Treger, McCullough, and Emmons[50] have reported 4 cases of systemic North American blastomycosis treated with intravenous amphotericin B. One of these 4 patients received only 110 mg. total amount of the drug. This does not represent an adequate amount of therapy. The other 3 received between 2.2 and 5.1 Gm. of amphotericin B in daily amounts varying between 30 and 45 mg. per dose. This averaged between 0.5 and 0.6 mg. per kilogram of body weight. These 3 patients are reported to have made apparent recovery, although an adequate follow-up time has not yet elapsed to evaluate these results thoroughly. Toxic symptoms in the form of

nausea, vomiting, marked anorexia, chills, and fever were reported in the same patients. Nevertheless, these authors conclude that amphotericin B is the drug of choice for disseminated North American blastomycosis.

Five of the 8 patients reported upon by us received but 1.0 Gm. of amphotericin B as a total dose. All 5 of these patients have apparently been cured, with a follow-up time varying from 11 to 29 months. Three of our 8 patients have had a relapse following amphotericin B therapy. One of these 3 was the first patient we treated with this antibiotic, and in retrospect we realize that he had received an inadequate amount of the drug when first treated. He was then given 1.0 Gm. of the drug, bringing his total dose to 1.5 Gm. He is apparently cured at the present time, being 26 months post treatment. The 2 other patients who suffered a relapse have received 4.0 and 4.5 Gm. of amphotericin B, respectively. These 2 patients had had widespread disease for many years prior to amphotericin B therapy. Each course of retreatment with this antibiotic has proved to be effective in producing temporary cessation of all signs and symptoms of active disease. These two patients are currently 14 and 15 months post treatment without evidence of active infection. It appears to us that a smaller total dosage of amphotericin B is required in the treatment of North American blastomycosis than is required in the therapy of any of the other systemic mycoses. The dosage of 50 mg. of amphotericin B given by slow intravenous drip, with the concomitant use of judicious amounts of steroid hormones and chlorpromazine at intervals of every other day, to a total dose of 1.0 Gm., represents the most effective means at hand of curing North American blastomycosis.

The oral form of amphotericin B is poorly absorbed, and, in spite of the one case[133] reporting benefit from such oral administration, we do not feel that this form of amphotericin B therapy should be given further trial.

Prior to the use of the aromatic diamidine and amphotericin B, a number of drugs had been tried for this disease. None of them have proved consistently effective. A saturated solution of potassium iodide administered orally and in increasing amounts had proved the only form of therapy which promised any beneficial effect. The cures which have been reported from the use of iodides usually occurred in individuals with the immunologic status of a positive blastomycin skin test and no complement fixing serum antibodies. More recently, Cornbleet[134] has advocated the use of a solution of potassium iodide plus thyroid extract in the treatment of North American blastomycosis. The 9 patients included in his report responded impressively to this form of therapy. There have been no follow-up or corroborative studies reported. There is doubt that there is any remaining place for iodide therapy or any of the older means of therapy advocated prior to the introduction of 2-hydroxystilbamidine.

South American blastomycosis

South American blastomycosis has been reported almost exclusively from South America, especially from Brazil. With increased opportunities for travel and greater population movements, however, cases may be encountered in countries distant from the known endemic areas, as exemplified by occasional reports from Germany,[135] Italy,[136] and the United States.[137,138]

The causative organism, *Blastomyces brasiliensis*, is a dimorphic fungus with filamentous growth at room temperature and yeastlike morphology at 37° C. The organism is characterized by multiple budding. Even though it has not been isolated yet from soil or plants, evidence points to a saprophytic phase in nature. The portal of entry is mainly the mucous membranes of the mouth, pharynx, or respiratory tract, accounting for the preponderant occurrence of the granulomatous lesions in these areas. From these locations, the infection disseminates through the blood stream and the lymphatic system to affect any organ, caus-

ing grave septicemic lesions. The lymph nodes and gastrointestinal tract are commonly involved. Lacaz[139] described the following anatomoclinical forms: (1) mucocutaneous, (2) ganglionary (lymphatic), (3) visceral, (4) mixed, and (5) blastomycosis associated with neoplasms and other infectious diseases.

Experience with the paracoccidioidin skin test and complement fixation test in South American blastomycosis is as yet limited and the results inconsistent.[57] Better standardization and more studies may yet prove these procedures as valuable in the diagnosis and prognostication of South American blastomycosis as of coccidioidomycosis, histoplasmosis, and North American blastomycosis.

Treatment. The prognosis of South American blastomycosis is generally grave. In some cases death may occur in 6 months, but the usual patient suffers through 2 to 4 years. The use of iodides, arsenicals, bismuth, gold, antimony, and certain dyes, like malachite green and methylene blue, had not modified significantly the serious course of the disease. However, since Ribeiro first treated a group of patients with sulfonamides in 1940 and obtained favorable results, the prognosis in this disease has been greatly improved. The response to sulfonamide therapy is satisfactory and the life expectancy of the patient is increased. Even biologic cures, though relatively few, have been claimed. To attain these, the administration of the drug must be early, intensive, and prolonged. Any of the sulfonamide preparations may be used singly or in combination. Sulfamerazine, Gantrisin, and, especially, sulfadiazine are preferred. The daily oral dose is 1 to 2 Gm. every 4 to 6 hours. In this way the effective blood level of 10 to 15 mg. per 100 ml. is attained and must be maintained continuously for long periods of time, even after apparent clinical cure. Relapses are common, particularly when administration of the drug is suspended. The recurrences are resistant to the resumption of therapy. The protracted administration of such large doses of sulfonamides that the total dose may reach even a few thousand grams entails the risk of toxicity. Periodic examinations for such toxic effects should be made.

In spite of the notable improvements attained with sulfonamides, the relapses, the toxicity of or intolerance to the drugs, the few actual mycologic cures, and the protracted therapy comprise the incentive to search for better agents. The antibacterial antibiotics are ineffective, as are ethyl vanillate[140] and nystatin.[141] Floch and Saccharin[142] claimed a clinical cure with 4,4′-diaminodiphenyl sulfone (DDS).

The hope that the favorable therapeutic effect of stilbamidine or 2-hydroxystilbamidine on North American blastomycosis would be of the same magnitude, if not greater, on South American blastomycosis has not been fulfilled. *Blastomyces brasiliensis* clinically has proved much less sensitive.[138,143,144] Another aromatic diamidine, diamidinodiphenylamine (M & B 938), proved to be more promising, however. MacKinnon, Sanjines, and Artagaveytia-Allende[144] tested six strains of *Blastomyces brasiliensis* and found the inhibitory concentration at 2 to 5 mcg. per milliliter of medium. They observed healing of oropharyngeal lesions and marked improvement of lung changes in a patient given two courses of daily intravenous injections of 150 mg. of M & B 938 with a total of 4 Gm. Another patient also showed definite improvement with a total of 5.475 Gm. in 43 days. There was no serious toxic reaction.[145]

In their initial studies of the in vitro antifungal spectrum of amphotericin B, Gold, Stout, Pagano, and Donovick and Sternberg, Wright, and Oura included *Blastomyces brasiliensis* which turned out to be sensitive. On the strength of these findings, Lacaz and Sampaio[146] treated 4 cases of South American blastomycosis with amphotericin B. The clinical results they obtained were so promising as to prompt them to state that a new era in the treatment of South American blastomycosis had opened with amphotericin B. Although kept alive by sulfonamide therapy, all 4 patients were essentially

refractive to the drug. One patient had taken more than 10,000 Gm. of sulfonamides in the course of 19 years, and another, 7,500 Gm. in 10 years. The relapses in each patient were controlled by amphotericin B with healing of the lesions, but no cure could be claimed, for the follow-up periods were still too brief.

Cryptococcosis

The true incidence of cryptococcosis is probably much higher than is indicated by the case reports in the literature of the severe pulmonary and meningoencephalitic forms with which most clinicians associate the disease. In the absence of a high index of suspicion and effective skin testing and serologic procedures, many of the benign, localized forms of cryptococcosis that simulate more commonly known diseases may go on to healing without being diagnosed. The condition has been reported from many countries and in both sexes and all ages.

The culturally and morphologically yeastlike organism, *Cryptococcus neoformans*, causes the disease. It is unique among the pathogenic fungi in the mucoid character of its colonies and the wide capsule surrounding its yeastlike body. The organism has been isolated from the skin and gastrointestinal tract of normal individuals, but more frequently from soil samples, especially those associated with pigeon and chicken droppings.[147,148] The infection may be endogenous, but probably more commonly results from an exogenous source through the respiratory tract and, occasionally, through the skin or gastrointestinal tract.

Because the vast majority of reported cases of cryptococcosis showed marked involvement of the central nervous system, the disease has become popularly associated with this particular form. In accord with the suspected mode of entrance of the organism through the respiratory tract, however, more and more attention has been directed to the pulmonary form of the disease. In many cases pulmonary complaints were registered at one time or another during the course of the illness. Although primary pulmonary cryptococcosis may at times cause death in a short time, the infection generally runs a benign, even subclinical, course with localized lesions that may resolve with or without minimal scarring. Eight of the 10 cases of pulmonary cryptococcosis described by Jacobs[149] revealed a solitary granulomatous nodule. These primary lesions in the lungs, whether active or healed, are frequently discovered only at autopsy on patients who die of the disseminated or meningitic form. The signs and symptoms of pulmonary cryptococcosis are those of chronic pneumonitis, lung tumor, or lung abscess.

With no regard to the course taken by the primary pulmonary condition, the infection may be disseminated hematogenously to other organs, with a predilection for the central nervous system. When this happens, the clinical picture becomes dominated by the central nervous system involvement, with signs and symptoms of meningeal irritation or increased intracranial pressure frequently misdiagnosed as tuberculous meningitis, brain tumor, brain abscess, or subarachnoidal hemorrhage. Involution of the pulmonary lesions may continue even in the face of this dissemination. Cryptococcosis of the central nervous system is almost always progressive, generally causing death in 3 to 4 months, sometimes in one year or so. However, unexplained remissions do occur and the patient may live up to 16 years, as in Beeson's[150] case.

Treatment. There is as yet no generally accepted effective treatment of disseminated cryptococcosis. Evans and Harrell[151] found that at least 43 methods, including the usual antibiotics, sulfonamides, x-rays, fever therapy, alkalinization, gold, copper, arsenicals, iodides, and vaccines, had been used. All proved essentially ineffectual. Except for amphotericin B, even the newer antifungal antibiotics and chemotherapeutic agents effective in vitro and in other mycotic infections give variable results, which suggests that possibly the apparent cures claimed for these drugs were actually spon-

taneous remissions. The observed resistance of *Cryptococcus neoformans* to drug therapy has been related to the thick capsule surrounding the organism.

Because of their in vitro activity[152,153] and demonstrated usefulness in the treatment of North American blastomycosis, the aromatic diamidines have been tried on clinical cases of cryptococcosis, in spite of failures in protecting laboratory animals against experimental infections.[154-156] Leithold, Reeder, and Baker[157] and Whitehill and Rawson[158] claimed apparent cure with 2-hydroxystilbamidine in one case each, and Ferguson[159] achieved marked improvement in another. The use of stilbamidine or propamidine, however, has been associated with clinical failure.[159-163]

Nystatin has been found active in vitro[164,165] and in animal experiments.[35,156,166] However, unlike its signal success in candidiasis, the few trials in human cryptococcic infections have thus far essentially failed to confirm such activity.[167-171] Perruchio, Bruel, Lagarde, and Delpy[172] used sulfadiazine and nystatin to treat a residual pulmonary lesion after resection in a 12-year-old girl. The sulfadiazine had to be stopped because of digestive intolerance but nystatin was administered for 20 days without trouble. The pulmonary lesion remained stationary.

Cycloheximide (actidione) is an antifungal antibiotic that has a selective marked in vitro activity against *Cryptococcus neoformans* among the pathogenic fungi.[35,164,173] It is not active, however, in experimental infections.[174] Likewise, in clinical trials only an occasional patient responded favorably.[175-178] The majority were not influenced and, in one instance, the drug might have even brought on an acute exacerbation of the disease and caused death.[167,179-185] The antibiotic is given intravenously, intrathecally, and/or intramuscularly. The initial dose is 20 mg., increased daily up to 100 to 200 mg. The intrathecal dose is 10 to 20 mg. The treatment is prolonged. Except for nausea and vomiting that may be severe, no serious toxicity has been observed.

In contrast with the other drugs, amphotericin B has exhibited a most encouraging activity. So far it is the most effective drug in the treatment of cryptococcosis and is apparently changing the gloomy outlook in this grave disease. It inhibits the organism in vitro at very low concentrations, down to a fraction of a microgram per milliliter of medium.[1,13,102] The increasing clinical use has consistently produced favorable results hitherto unknown in the management of cryptococcosis. Thus far, at least 49 patients, the majority of whom had central nervous system involvement, have been reported treated with amphotericin B.[11,16,50,91,110,168,171,186-197] Apparent clinical remissions were claimed in 17 cases with follow-up periods of from 4 to 18 months. Nineteen improved in varying degrees, with 8 noted as having attained conversion of the cultures for the organism to negative. Three patients were reported unimproved, but in 2 of them the drug was administered mainly by the oral route. Two relapses and 8 deaths occurred, but in 6 cases medication was instituted late in the course of the disease a short time before death, and the authors expressed the opinion in each case that the treatment was not given a fair trial. In one case the organism disappeared from the spinal fluid, and death was blamed on bacteremia and renal failure.

Surgical intervention has a definite place in the management of cryptococcosis, being particularly indicated for excision of early, localized lesions before dissemination occurs.[198-202] The resection of primary lesions has been attempted even in the presence of spread to the central nervous system in the hope of preventing further seeding from these primary foci.

Actinomycosis

Actinomycosis is a subacute to chronic suppurative granulomatous disease characterized by brawny inflammatory lesions, abscess formation, and multiple draining sinuses and fistulas. It is world-wide in distribution with no racial predilection and affects all ages, especially young adults.

The single causative organism is *Actinomyces israeli* (syn. *Actinomyces bovis*) which is gram positive, non-acid fast, branching, filamentous, and anaerobic. The diagnostic "sulfur granules" found in the exudate from the abscesses or draining lesions are dense networks of the filamentous organism radially arranged, with clublike endings.

Actinomyces israeli has been isolated from the gums, periodontal pockets, and peritonsillar crypts of normal individuals. The infection is apparently endogenous, with trauma or disease as contributory factors related to lowered local tissue resistance and acquired pathogenicity of the organism. "Mixed infection" with other symbiotic bacteria, as *Actinobacillus actinomycetem-comitans, Bacterium melaninogenicum,* and anaerobic streptococci has been implicated as part of a pathogenic complex with *Actinomyces israeli.*[203-206]

A wide variety of signs and symptoms is observed in actinomycosis depending upon the part of the body invaded. The three main clinical types are (1) cervicofacial, comprising more than half of the reported cases, (2) abdominal, 20 per cent, and (3) thoracic, 15 per cent. The rest of the cases present involvement of other parts of the body such as the extremities, liver, genitals, kidneys, skin, bones, joints, or central nervous system. Spread of the infection is by direct invasion. The prognosis of cervicofacial actinomycosis is generally much better than that of the abdominal or thoracic types.

Treatment. Before the advent of sulfonamides and penicillin in the treatment of actinomycosis, a multitude of therapeutic measures (including iodides, x-rays, surgical procedures, vaccines, copper salts, thymol, gold, arsenicals, and others) were utilized with varying results. Singly, they were ineffective, especially in the abdominal and thoracic forms of the disease. Even in combination, most of the reports of their favorable use were on cases of cervicofacial actinomycosis which has a relatively fair prognosis, even without therapy. Many of these older methods have been discarded except for a few, such as iodides and x-rays, which are retained by some as helpful adjunctive measures to penicillin treatment.

Although later proved to be less effective than penicillin and the other antibiotics in vitro[207,208] and in clinical treatment,[209-211] the sulfonamides gave the first consistent favorable results in the treatment of actinomycosis and improved the prognosis of the disease during the years following its introduction in 1937. Better results were achieved when these drugs were combined with adjunctive treatment, such as surgical intervention, iodides, or x-rays. Of the sulfonamides, sulfadiazine and sulfisoxasole are the better preparations.[212] Oral doses of 3 to 4 Gm. daily with effective blood levels of 8 to 10 mg. per 100 ml. should be maintained through a period of 4 to 6 months or longer. The usual precautions against possible toxicity must be observed.

Penicillin was introduced in 1945 and has steadily supplanted the sulfonamides. The actinomycete is most sensitive to penicillin in vitro,[213-215] and a host of successful clinical reports testify to the superior efficacy of penicillin. Although in many of these reports penicillin was combined with other therapeutic measures, the antibiotic unquestionably has augmented the rate of recovery, especially in the graver abdominal and thoracic forms. There are still treatment failures, however, in spite of the demonstrated sensitivity of the organism to the antibiotic. The very nature of the disease process with its excessive formation of granulomatous and fibrous tissues impedes the effective concentration of the drug in the diseased area. This necessitates the administration of large doses for prolonged periods and the aid afforded by adjunctive therapy, such as surgical measures and iodides. Another suggested reason for these treatment failures is the penicillin resistances of certain bacteria like *Actinobacillus actinomycetem-comitans* comprising part of the symbiotic flora responsible for the concomitant infection in actinomycosis.

The recommended average dose of peni-

cillin is 3 to 6 million units daily for at least 3 months, extending even to 12 to 18 months, depending upon the response of the patient.

The need for another effective drug that can be used in place of penicillin has been felt for several reasons: (1) the cases that appear to be resistant to penicillin treatment, (2) the increasing incidence of sensitization to penicillin, and (3) the objections to repeated parenteral injections over long periods of time. The newer broad spectrum antibiotics and other chemotherapeutic drugs have been investigated and successfully used. They include streptomycin, tetracycline, oxytetracycline, chlortetracycline, erythromycin, chloramphenicol, isoniazid, and stilbamidine. It is still quite early to confirm the exact value of these drugs. Erythromycin, at least in vitro, is the most effective. Their main disadvantages, especially those of the broad-spectrum antibiotics, are their toxicity and their high cost as compared with penicillin.

Surgical measures are generally admitted to be of considerable value, if not curative as in localized lesions. The procedures range from simple aspiration of fluid to radical complete excision of diseased organs, as pneumonectomy, nephrectomy, or resection of intestines. Better results are obtained when these are associated with drug therapy.

Only a small number of reported cases of actinomycosis were managed with a single mode of therapy. Most were given multiple treatments with preference for penicillin, combined with sulfonamides or any one of the other antibiotics and chemotherapeutic drugs, iodides, x-rays, and surgical procedures. Because of strain variation[207,214,216] the desirability of sensitivity tests performed on the actinomycetes and the symbiotic bacteria isolated from the actinomycotic lesions to determine the proper drugs to be administered has been stressed.

Nocardiosis

Nocardiosis is closely akin to actinomycosis clinically and mycologically, but with enough differences to separate it from the latter condition as a distinct entity. The causative organisms belong to the Nocardia genus which is widely distributed in nature and frequently isolated from soil. There are at least five species known to be pathogenic to man,[217,218] including *Nocardia asteroides, Norcardia brasiliensis, Norcardia madurae,* and *Nocardia pelletieri.* By far the most common is *Nocardia asteroides.* These organisms are gram positive, variably acid fast branching filaments, readily fragmenting into bacillary and coccoid forms. They grow aerobically.

The disease is world-wide in distribution with no racial preference. The source of infection is exogenous. The most frequent portal of entry is the respiratory tract and, less commonly, the injured skin and the gastrointestinal tract. Thus, many of the cases (about 75 per cent) reveal pulmonary involvement. The pulmonary form presents the clinical picture of acute or chronic pneumonitis, with a propensity for hematogenous dissemination to other organs, particularly the central nervous system. Once the central nervous system becomes involved, which occurs in about 30 per cent of the cases, the pulmonary complaints are overshadowed by signs and symptoms simulating brain tumor, brain abscess, or meningitis, and the prognosis becomes graver. The disease may be acute and fulminating, causing death in a few days, but generally it tends to be chronic, with remissions and exacerbations lasting for even up to 3 to 4 years. The average duration is 6 months.

A chronic and localized form of nocardiosis involving the skin and subcutaneous tissues constitutes a certain percentage of the incidence of maduromycosis or mycetoma. The granules found in the discharge from the multiple draining sinuses and fistulas are smaller and softer than the "sulfur granules" of actinomycosis. They are colored black, red, orange, or yellow and do not present clublike terminal structures at the periphery.

In many cases the diagnosis of nocardiosis was made only after operation, very late

in the course of the disease, or at the autopsy table. Definite diagnosis can be made only with the laboratory demonstration of the organism.

Treatment. The particular importance of early diagnosis and institution of treatment in nocardiosis has been emphasized, in view of the remarkable clinical efficacy of the sulfonamides, especially sulfadiazine. Most of the unsuccessful clinical trials with sulfonamides were blamed on the failure to establish an etiological diagnosis and start medication before the disease had become disseminated and progressed to an advanced stage. The sensitivity of *Nocardia asteroides* to sulfonamides has been amply confirmed in vitro[219-224] and in vivo[207,261] and by apparent clinical cures achieved. The effective blood serum level of sulfadiazine is 10 to 20 mg. per 100 ml. with daily oral doses of 6 to 10 Gm. maintained over prolonged periods of time from 3 to 6 months or longer.

The sulfonamides have usually been used in conjunction with other measures, such as surgical intervention, x-rays, iodides, thymol, broad-spectrum antibiotics, and even penicillin (which has been shown to be ineffective, in contrast to its success in the management of actinomycosis). In the choice of antibiotics and other chemotherapeutic agents, in vitro sensitivity tests may be misleading, for their results do not seem to correlate with those of clinical experience. A patient with pulmonary nocardiosis described by Rivera[223] failed to respond to tetracycline but improved with chloramphenicol, although in vitro the isolated Nocardia was found to be sensitive to tetracycline and resistant to chloramphenicol. Both Runyon[222] and Halde and Newstrand[216] found streptomycin to be effective in vitro, but inactive in animal experimental infections. Nonetheless, sensitivity tests are still considered useful by the latter authors. In general, the clinical results with antibiotics and other agents like isoniazid, pregnenolone acetate, or stilbamidine without sulfonamides have been variable.

The sulfones have been shown to be active against the Nocardias.[216,225-227] González Ochoa and his group, who have spearheaded these investigations, worked on the premise that Promin, Promizole, and Diasone act in vivo mainly by breaking down into 4,4′-diaminodiphenyl sulfone (DDS). They concentrated on DDS and found it effective, particularly in infections with *Nocardia brasiliensis.* Of 21 patients with 4 year follow-up periods, 15 were cured and 6 showed marked improvement. The treatment was prolonged: at least 2 years of daily oral administration of 200 mg. Premature withdrawal of the drug led to relapses which were much more resistant to subsequent treatment. The drug was also injected locally into the tumor mass or into the fistulas in 2 ml. amounts of 20 per cent solution daily. In spite of the long-term administration, surprisingly few serious toxic reactions appeared, except for secondary anemia which was easily controlled with iron therapy.

Surgical intervention is still definitely indicated in the management of nocardial infections, particularly in the mycetomatous form.[228] Drainage of abscesses and excision of involved tissues are important adjuncts to sulfonamide therapy.

Sporotrichosis

Sporotrichosis is most often a subcutaneous rather than a systemic or deep fungus infection. The disease normally assumes the rather typical clinical appearance of an ulcerating, granulomatous, chancriform lesion, occurring at the site of direct cutaneous inoculation. The development of satellite lymphangitis and nodules occurring along the inflamed lymphatics is also typical of the disease. The marked variations which occasionally occur in the cutaneous and subcutaneous forms of sporotrichosis demand that all clinicians maintain a high index of suspicion for this particular fungus disease. Systemic involvement may develop from *Sporotrichum schenckii* infection from a cutaneous site. Involvement of almost any organ with sporotrichum may

occur. It has been reported in the kidneys, testicles, epididymis, muscles, bones, joints and tendons, lungs, central nervous system, and tracheobronchial lymph nodes.[25]

Sporotrichum schenckii is found with great difficulty on microscopic examination of stained or unstained clinical material. A positive diagnosis of sporotrichosis can be established only by culture of *Sporotrichum schenckii* on suitable media. Fortunately, this organism is not fastidious in its nutritional requirements, and a brownish to blackish, wrinkled, leathery-appearing colony grows out readily on routine Sabouraud's glucose agar at room temperature, while a white, wrinkled, cerebriform, bacteria-like colony develops on the blood agar cultures at 37° C. This latter culture exhibits the budding yeast phase growth of the organism, while the room temperature culture exhibits hyphal growth with clusters of typical small pyriform conidia.

Treatment. The iodides have become well established as the treatment of choice for sporotrichosis of all types.[25] Invariably, a favorable response can be obtained by the oral administration of increasing doses of a saturated solution of potassium iodide. The initial dose should be approximately 5 drops given 3 times a day. This may be increased by one drop per dose, if a rapid increase is desired, or one drop per day otherwise, until the dosage of 40 to 50 drops 3 times a day is attained. This amount should be maintained for at least 2 to 3 weeks beyond the time that complete clinical healing has occurred. The patient should be instructed that clinical improvement is not to be expected until the iodides have been given for 2 to 3 weeks' time. Only rarely is this form of therapy ineffective in producing complete cure of any type of sporotrichosis. It is puzzling that the iodides have such effect on this fungus, for there is no evidence of increased uptake of radioactive iodine at the site of sporotrichotic lesions in the skin. The organism also grows in artificial media containing 10 per cent concentration of potassium iodide.[25] The iodides will not prevent experimental infection of the rat, although they will effect cure of rat sporotrichosis, if continued in adequate dosage.[229]

The aromatic diamidines, and particularly 2-hydroxystilbamidine, deserve consideration in the therapy of systemic sporotrichosis. An excellent in vitro effect against *Sporotrichum schenckii* has been demonstrated,[152,230] and sporotrichosis has successfully been treated with stilbamidine.[231] One case of central nervous system sporotrichosis has been treated with 2-hydroxystilbamidine.[232] This patient was not able to tolerate the aromatic diamidine and died of renal insufficiency coincident with the drug therapy. Necropsy revealed healing lesions of sporotrichosis. We have seen a patient with sporotrichotic involvement of a knee joint who had a relapse following 2-hydroxystilbamidine therapy. This patient was re-treated with amphotericin B in amounts of 50 mg. administered by slow intravenous drip in 500 c.c. of 5 per cent glucose in water at daily intervals. A total dose of 0.5 Gm. was given. Following this therapy, the sporotrichotic arthritis was no longer evident, and cultures of the joint space were negative for *Sporotrichum schenckii.* We have since learned that this patient has suffered a clinical relapse of the joint sporotrichosis. Amphotericin B has a high in vitro inhibiting effect on *Sporotrichum schenckii.*[1,102] It is probable that this antibiotic would be effective in causing prompt cure of the usual type of uncomplicated lymphatic sporotrichosis. It is doubtful that this toxic antibiotic should be given for the routine, benign forms of sporotrichosis.

Candidiasis

Candidiasis is not usually considered one of the deep or systemic mycoses. This disease (which was previously called moniliasis) is caused by members of the genus Candida, usually *Candida albicans.* This yeastlike fungus can be isolated from normal stool, the vagina, the oral mucous membrane, the skin, and even the normal external auditory canal.[233] It is normally the

cause of superficial infection in mucous membranes of the mouth, the vagina, the paronychial skin, as well as the glabrous skin of the warm, intertriginous areas of the body. *Candida albicans* is rarely reported as the cause of truly systemic disease. Its incidence has sharply increased, however, with the increased usage of broad-spectrum antibiotics and the steroid hormones. These two categories of therapeutic agents have increased human susceptibility to systemic infection with *Candida albicans*.[234-237] Since the fungus is often not pathogenic, there is also a problem associated with the clinical interpretation of the laboratory isolation of *Candida albicans* from such clinical sources as sputum, urine, skin and nail scrapings, nasopharyngeal scrapings, and gastric contents. The finding of *Candida albicans* or other species of Candida on blood culture leaves no question as to pathogenicity.[235]

The members of the Candida genus are easily cultured on almost any of the standard bacteriologic agars or media. *Candida albicans* is separated from the other species of Candida by the findings of terminal chlamydospores in the submerged portion of the culture when grown on corn meal agar. The finding of hyphal growth along with the single-budding blastospores in sputum, scrapings of skin or mucous membranes, and urine is quite significant, and probably indicates that this yeastlike fungus has assumed the role of a true pathogen. *Candida albicans* is a pathogenic opportunist and is found as a superimposed infection in individuals with debilitating diseases, pregnancy, uncontrolled diabetes mellitus, the avitaminoses, and, as previously mentioned, those who are receiving long-term steroid or intensive antibiotic therapy. There is no reliable skin test which can be performed to aid in the diagnosis of candidiasis, and even though agglutinins have been demonstrated as part of systemic candidiasis, their presence has not been reliably consistent.

Treatment. Two antifungal antibiotics must be given consideration in the treatment of systemic candidiasis. Nystatin and amphotericin B have both demonstrated excellent in vitro and in vivo effect against *Candida albicans*.[12,35,50,235,237-243] Nystatin, an antibiotic substance obtained from a species of streptomyces, is very effective in curing candidiasis when it is possible to apply the antibiotic directly to the causative fungus. This is quite possible when the patient has infection of the skin or mucocutaneous junction, the mouth or pharynx, the vagina, or the gastrointestinal tract.[237,240,243] Unfortunately, nystatin is very poorly absorbed from the gastrointestinal tract, and it is impossible to obtain adequate blood levels of this drug when given by this route. Nystatin has not proved effective in controlling or curing pulmonary or bronchopulmonary candidiasis or Candida septicemia. There is one report[235] of systemic candidiasis complicating bacterial endocarditis with apparent cure following the use of intramuscular nystatin in the dose of 9.6 million units administered over a 16 day period. Unfortunately, nystatin given intramuscularly causes marked pain, swelling, and abscess formation at the site of injection. This form of the antibiotic is no longer available. However, nystatin is, without question, the drug of choice for candidiasis of any type when it is possible to use the antibiotic in ointment, lotion, mouth wash, wet dressing, suppository, or tablet form.

Amphotericin B administered intravenously must be considered as the probable therapy of choice for pulmonary candidasis and Candida septicemia. Like nystatin, amphotericin B is very poorly absorbed from the gastrointestinal tract when given orally. Also, like nystatin, amphotericin B produces a marked decrease in the number of *Candida albicans* organisms in the gastrointestinal tract, even when it is administered with a broad-spectrum antibiotic such as tetracycline.[12] There is but one report of the use of intravenous amphotericin B in systemic candidiasis. Utz, Treger, McCullough, and Emmons[50] report the use of this antibiotic in 4 cases. Three of the 4 patients had previously undergone major surgical procedures; 2 developed Candida endocar-

ditis following cardiac surgery, and one developed meningeal candidiasis following an operation for the insertion of a Holter valve to relieve a noncommunicating hydrocephalus. The 3 surgical patients died of candidiasis; however, it is doubtful that they received an adequate trial of amphotericin B therapy. In a fourth case reported by the same authors Candida sepsis followed cystoscopy and retrograde pyelogram for a renal calculus. Blood and urine cultures were positive for *Candida albicans.* Complete recovery ensued after the patient was given a total of 110 mg. of amphotericin B over a 4 day period of time. There is good indication that amphotericin B is effective in the most serious forms of candidiasis.

Two other chemotherapeutic agents deserve definite consideration in the treatment of systemic candidiasis. A saturated solution of potassium iodide has been used for many years as an adjunct in the treatment of all types of candidiasis.[25] This should be given orally. The initial dose is 5 drops 3 times a day following meals, with increments of one drop for each dose, until the total dose of 20 drops 3 times a day is reached and maintained. We are dubious of any true benefit to be obtained in systemic candidiasis from potassium iodide therapy. The careful intravenous administration of methylrosaniline chloride (gentian violet) appears still to be worthy of consideration.[244,245] While the topical application of this dye was the chief means of controlling superficial candidiasis prior to the development of nystatin, methylrosaniline chloride is recommended in intravenous dosage of 5 mg. per kilogram of body weight, given every other day for 7 to 10 days. Concentration of the dye should not exceed 0.5 per cent and the solution should be filtered through a Berkefeld or Seitz filter.

A host of other chemotherapeutic agents have been advocated for the treatment of cutaneous and systemic candidiasis. These include such agents as fatty acid, resin complex,[246] the para-aminobenzoic acid esters,[247] vitamin B complex, brilliant cresol green, the aromatic diamidines, testosterone, methyltestosterone, testosterone propionate, and even broad-spectrum antibiotics.[248] It should be mentioned, also, that the new antifungal antibiotic, griseofulvin, has shown no in vitro nor in vivo effect against *Candida albicans* or other members of the candida genus. We have had occasion to use griseofulvin in widespread cutaneous candidiasis and have not observed beneficial effect.

Aspergillosis

The aspergilli abound in nature. Palinologic surveys have shown the prevalence of their anemophilic spores in the atmosphere, where they form one of the aerobiologic factors causing inhalant allergy. The fungus is well known as a saprophyte but can be parasitic to plants, birds, and occasionally, mammals. Of the more than 375 species described, only a few have been isolated as pathogens for man: *Aspergillus fumigatus,* by far the most common; *Aspergillus glaucus; Aspergillus flavus; Aspergillus niger;* and *Aspergillus nidulans.*

The fungous growth is mycelial and characterized by a knoblike fruiting body to which numerous conidia are attached. The tissue form is morphologically the same as the saprophytic phase.

For reasons still not known exactly, the fungus occasionally acquires the ability to invade tissues, causing granulomatous lesions in the lungs, skin, external ears, nasal sinuses, nails, central nervous system, eyes, bones, and vagina. The organism may be a primary or secondary invader. The symptomatology varies with the areas involved, such as that of pneumonitis, onychomycosis, otitis externa, or maduromycosis. The most common form is otomycosis, but pulmonary aspergillosis has gained more medical interest. Primary pulmonary aspergillosis is usually regarded as an occupational disease among individuals unduly exposed to the spores. A significant number of cases of pulmonary aspergillosis is superimposed as a secondary infection on other diseases, such as tuberculosis, carcinoma, bronchiectasis, or infarction. The infection is rarely dissem-

inated.[249] The clinical picture is that of tracheobronchitis, bronchopneumonia, tuberculosis, or tumor. The x-ray findings vary considerably and may show a "sunburst effect," evidence of pneumonic or bronchopneumonic consolidation, cavitation, or, rarely, a diagnostic solitary density whose superior border is outlined by a thin, crescent-shaped area of radiotranslucency.

A definitive diagnosis of aspergillosis is difficult to make and cannot be established on clinical grounds alone. It depends on the demonstration of the organism from the clinical material. Even the cultural isolation of the fungus does not answer the question of whether the isolated organism is a pathogenic invader or a contaminant. The diagnostic criteria are repeated isolations of the aspergillus in pure cultures from the lesions and its demonstration histopathologically with the surrounding tissue reaction of the body.

Together with infections due to organisms generally known as saprophytes, like Mucor, Candida, Geotrichum, and Penicillium, aspergillosis has increased in incidence associated with the present-day extensive use of steroids and broad-spectrum antibiotics.[250,251] Sidransky and Friedman[250] made mice highly susceptible to fatal pulmonary aspergillosis by treatment with steroids and antibiotics. The inhaled spores failed to germinate into hyphae in the control mice, but did so readily in the treated animals. The steroids apparently were more responsible.

Treatment. There is no consistently effective medical control. The noted increased incidence of aspergillosis has made the search for the ideal chemotherapeutic agent more imperative. The occasional favorable results obtained with sulfonamides, penicillin, streptomycin, and other antibiotics were attributed mainly to their action on concomitant bacterial infections.

The in vitro sensitivity of *Aspergillus fumigatus* to certain antibiotics and chemotherapeutic agents has occasionally been studied.[252,253] The marked sensitivity of the organism to mercuric iodide red was noted. Penicillin was inactive in concentrations up to 125 μg per milliliter of medium, but inhibited fructification above this concentration. Even at 10 mg. per milliliter of medium, the broad-spectrum antibiotics succeeded only in preventing fructification.

There is a paucity of clinical reports on adequate therapeutic trials in aspergillosis because of the difficulty of establishing a preoperative or antemortem diagnosis. As a result, the data are grossly insufficient and the conclusions as to the value of the drugs tested are at most preliminary.

The aromatic diamidines were tried in a few cases. Riddell[254] stated that, in his experience, inhalation of 2-hydroxystilbamidine solutions was effective in removing *Aspergillus fumigatus* from bronchial secretions. Stevenson[255] reported a case of pulmonary aspergillosis which responded satisfactorily to two courses of 10 intravenous injections of 150 mg. of 2-hydroxystilbamidine given daily. This therapy was followed by a course of oral nystatin. The patient, however, died later with renal failure. A patient with primary pulmonary aspergillosis described by Librach[256] did not respond to treatment with 2-hydroxystilbamidine as well as to iodides, isoniazid, streptomycin, penicillin, and oxytetracycline. Hinson,[252] on finding that *Aspergillus fumigatus* was inhibited in vitro by diamidinodiphenylamine (M & B 938) in a concentration of 1:100,000, tried the drug clinically in a case of pulmonary aspergillosis. The patient showed only slight equivocal improvement and severe toxic hypotensive symptoms with administration of the drug.

The agent being sought for the effective control of aspergillosis most probably will be found among the antifungal antibiotics that are being introduced in increasing numbers. Riddell[254] also mentioned the effective use of nystatin inhalation. Stevenson's[255] patient also received nystatin, 500,000 units given thrice daily for 8 weeks, after two courses of 2-hydroxystilbamidine. In the successful treatment of a case of hypopyon keratitis due to *Aspergillus fumigatus,* Mangiaracine[257] believed that ny-

statin administered locally and systemically exerted a beneficial effect. Manning and Robertson[258] recently described a case of pyopneumothorax due to a secondary infection with *Aspergillus fumigatus* after a history of treated pulmonary tuberculosis and a bout of secondary pneumococcal infection for which the patient had received a course of tetracycline. Nystatin was administered by intrapleural instillation of 500,000 units daily. The patient received 15.5 million units in 38 days and improved remarkably, with no side effects due to the drug. The organism disappeared from the sputum. A concomitant secondary infection with *Staphylococcus aureus* was controlled with daily intrapleural administration of 0.5 Gm. chloramphenicol.

An antifungal antibiotic that deserves clinical trial in aspergillosis is griseofulvin, which has aroused interest because of its efficacy in the treatment of dermatomycosis by the oral route.[259,260] Its inhibitory effect on filamentous fungi with chitin cell walls which include the aspergilli is most specific.[261] The antibiotic is relatively nontoxic in therapeutic doses. It is not unreasonable to predict that favorable results will be obtained with the use of griseofulvin in aspergillosis, particularly in its otomycotic and onychomycotic forms, in view of its affinity for keratinous tissues.

In the absence of successful medical treatment in aspergillosis, emphasis is laid on the surgical approach. This is mainly excisional in nature, and most reports of apparent cures in aspergillosis deal with the resection of localized lesions, such as aspergillomas.[262-264]

Mucormycosis

Systemic disease produced by members of the order Mucorales is referred to as a mucormycosis, even though members of the genera *Rhizopus, Absidia,* and others, besides the genus Mucor, may cause the disease. The name mucormycosis is quite acceptable when used in this manner. This is fortunately a rare mycotic disease, which usually develops in individuals who have uncontrolled diabetes mellitus. The disease was first reported by Paltauf[265] in 1885. Since that time, there has been a total of 24 cases of mucormycosis reported in the world's literature.[266,267] A complete summary of the reported cases of mucormycosis is available.[266]

The members of the order Mucorales most commonly found to produce mucormycosis are Rhizopus sp. and Mucor sp. Both of these fungi occur as common laboratory contaminants, and are known as "sugar fungi."[268,269] The hyphae of these fungi exhibit few or no septations and possess the ability to break down sugar. It is of interest that they have been found to be most pathogenic in diabetic individuals. They grow at a very rapid rate and, when contamination with Mucor sp. or Rhizopus sp. occurs, it takes but a few days for the aerial growth of the organisms to fill completely all the available space of the culture tube. The tendency toward such rapid growth has been exhibited clinically when these contaminant fungi assume pathogenicity. Extension through the orbit or paranasal sinuses to the cerebral vessels has occurred in the vast majority of cases,[266,269] and in most instances death has occurred within a matter of days from the time symptoms have been reported. The syndrome consisting of diabetes mellitus, ophthalmoplegia, signs of meningoencephalitis, and possibly sinusitis should make one consider the diagnosis of cerebral mucormycosis.[269]

There are no instances of successful attempts at chemotherapy for mucormycosis. A case has recently been reported[266] in which potassium iodide, given during a 48 hour period prior to death, had no beneficial effect. Unfortunately, this disease is usually diagnosed post mortem, and amphotericin B has not been given an adequate trial. This antifungal antibiotic should be given a therapeutic trial in any individual in whom the antemortem diagnosis of mucormycosis has been established. Chick[270] has treated experimentally produced mucormycosis in rabbits with amphotericin B. The drug was found to protect a rabbit

which had been given a standardized lethal dose of Rhizopus spores. Also, the drug apparently inhibited the transformation of spores into hyphae, when injected intravenously. The animals that were sacrificed following such injections were found to be virtually free of evidence of visceral infection. These experiments suggest that amphotericin B may be of great value in the treatment of human mucormycosis.

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