The Magnitude of the Public Health Problem Posed by the Mycoses

Part II: The Lack of Information

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Presently, it is obvious that mycotic infection are common in Thailand. However, there is a problem with nonrecognition or delay in recognition of these diseases. This communication is the second part of a report on the magnitude of the public health problem caused by the mycoses in Thailand. The purpose of the report is to reveal the current status of ongoing research and the available information on mycotic infections in Thailand.

THE SUPERFICIAL MYCOSES

Superficial infections caused by fungi are limited to the outermost keratinized layer of the skin. Due to the absence of penetration inflammatory responses do not occur. The most common superficial infection seen is Pityriasis versicolor, which is often found on the trunk and upper parts of body. Black piedra, an infection of the hair, is occasionally seen.

THE CUTANEOUS MYCOSES

There are very few formal reports on cutaneous infections caused by fungi in Thailand. The information available is mainly obtained by personal communication. For infections produced by the dermatophytes, the most common sites involved are the trunk (20%), face (19.5%), groin (19.5%) and feet (12%). Tinea nigra, an infection of the palms and soles caused by Phaeoannelomyces (Exophiala) werneckii, is not commonly seen. The current analysis of causative organisms shows no obvious regional differences in the prevalence of organisms. In Bangkok, Trichophyton rubrum accounts for 60% of the culturely proven infections. The other dermatophytes in descending frequency are T. mentagrophytes and Epidermophyton floccosum. In the north, the leading organism is also T. rubrum. It accounts for 73 per cent of all isolations, while T. mentagrophytes is second at 10 per cent and Epidermophyton floccosum third at 3.37 per cent. Microsporum gypseum has not been reported. Personal communications suggest that M. audouinii is quite often seen in northeastern Thailand, but that it is very rare in central and northern Thailand. Epidemics of scalp ringworm occur among religious novices, since they live under closely crowded conditions.1 Tinea imbicata, which is caused by T. concentricum, an anthropophilic dermatophyte, was commonly seen in Thai villages in the preceding three decades.2 Today it is uncommon.3 Oral thrush and vaginal candidiasis are common infections. The risk of acquiring a Candida infection is increased in a hospital environment and the incidence rises during hospital residence. However, the acquisition of a Candida infection is not necessarily related to hospital admission. Vaginal candidiasis seems to have increased in recent years. For instance, in a cancer survey of rural woman at Amphur Ban-Na, Nakornnayok, a province, near Bangkok, about
3,000 women were vaginally examined and pap smeared and 3.6 per cent were found to have candidiasis. From 200 cultures randomly obtained, 15% were positive for a Candida sp. and 25 per cent of these were from patients using contraceptive pills or devices. Thus, it seems that vaginal candidiasis in Thailand, as elsewhere, is not only associated with diabetes mellitus and pregnancy, but also with contraception. However, changing attitudes concerning sexual activity should also be considered as contributing factors in the increase of candidiasis.

THE SUBCUTANEOUS MYCOSES

Subcutaneous infections caused by fungi are not common in Thailand. However, they are clinically important because of their chronicity and the tissue destruction that they cause. The causative organisms are often resistant to therapy and prone to fatal dissemination in immunocompromised patients. Unfortunately, little information is found in the Thai literature and the few descriptions of cases included in this communication were obtained from a recent review of patient records and by personal communications.

Mycetoma

Mycetomas arise from traumatic implantation of potentially pathogenic soil fungi and aerobic actinomycetes into exposed parts of the human body. The original site of inoculation often escapes notice until it becomes abscessed and a discharge arises from a draining sinus in which the fungal elements appear as "grains". Infections in this group are somewhat confusing because they are caused by two diverse groups of etiologic agents. The first group comprises higher bacteria, the Actinomycetes, which until recently, were historically classified with the fungi. However, it is indeed important to realize that they are not fungi since they are susceptible to antibacterial agents such as penicillin and the sulfonamides, which are not active against the pathogenic fungi. This group of infections is more accurately called actinomycotic mycetomas. The second group of agents comprises true fungi. The diseases that they cause are called eumycotic mycetomas. The gross clinical symptoms for both groups are indistinguishable, as they appear as granulomas which eventually undergo tumefaction and produce draining sinuses that discharge granules.

In Thailand, the first mycetoma case was briefly reported in 1928. The second case was reported in a young farmer in 1936. The lesion appeared as an abscess at the iliac crest and spread to the lower abdomen with draining sinuses. However, isolation of the etiologic agent was not carried out. Since then, a few cases have been reported with various etiologic agents some of which are also known to be agents of other mycoses. These fungi are Pseudallescheria (Alleschera) boydii, Scedosporium (Monosporium) apiospermum, and Exophiala (Phialophora) Jeaneli.

In 1980 a series of 17 cases was reported by the Institute of Dermatology. The common infection sites were the legs, ankles and feet. Rare lesions were found on the fingers, buttocks and shoulders. Seven cases had bone involvement. Only eight cases were confirmed by culture. Among the etiologic agents identified were Nocardia asteroides, N. brasiliensis, N. otitidis-caviarum (N. cavia) and Actinomadura (Streptomyces) madurae. The true fungi included in this report were: Madurella mycetomatis, Pseudallescheria (Alleschera) boydii, Acremonium (Cephalosporium) falciforme and Neotestudina rosa-tii. In this series of cases, the traumatic sites of entry were not recorded. At Ramathibodi Hospital in 1983, there was a case of a Thai male aged 34 who lacerated his knee during a car accident in the mountains. The wound healed well following suturing but one week later he developed septic arthritis caused by Pseudallescheria boydii. He was successfully treated with patellectomy and therapy with miconazole, using a total dose of 20 gms, over a 26 day period. In this case, the history suggested soil contamination of the wound whereby the fungus gained entrance to the knee.

Chromoblastomycosis

Chromoblastomycosis is a subcutaneous fungal infection caused by five species of dematiaceous fungi (pigmented fungi). The term chromomycosis was used instead of chromoblastomycosis by Moore and Almeida as they felt that the term chromoblastomycosis was misleading as it implied that the etiologic agents grew as yeasts in tissue. Problems in nomenclature of this disease occurred when some individuals inappropriately expanded the original concept of chromoblastomycosis to include other mycoses caused by several different genera and species of dematiaceous fungi, for which they have incorrectly applied the term "chromomycosis". To correct this problems, Ajello et al. created the name "phaeohyphomycosis" for those infections that are clinically, pathologically, and mycologically distinct from classical chromoblastomycosis. Phaeohyphomycosis will be described in the last part of this paper.

The etiologic agents of chromoblastomycosis are Fonsecaea pedrosoi, F. compacta, Phialophora verrucosa, Rhinocadiella aquaspersa and Cladosporium carrioni. These moulds gain entrance; like other subcutaneous pathogens, through the skin by traumatic implantation. The primary lesions of chromoblastomycosis therefore frequently develop on the foot or leg. The lesions are limited to the cutaneous and subcutaneous tissues and begin as small pink scaly papules which gradually increase in size to form superficial
nodules. The tissue response is mainly hyperplasia which results in verrucoid, warty cutaneous nodules which may, after months or years, appear as pedunculated and verrucous lesions that resemble the florets of a cauliflower. Spread along the lymphatic channels can result in a new crop of lesions. In advanced cases, extensive fibrosis often blocks the lymphatics, causing lymphostasis, and resulting in edema of the legs and feet, that resembles elephantiasis. Histopathology reveals hyperplasia of the epidermis which may become pseudoepitheliomatosus, with dermal granulomas, intraepidermal microabscesses and fibrosis. Dematiaceous hyphae may be present in the epidermis. However, the diagnostic feature of chromoblastomycosis is the presence of muriform cells, the so-called sclerotic bodies, which are spherical or polyhedral, dark, thick-walled, partitioned in one or two planes and which measure 5-12 μm in diameter. The muriform cells apparently represent an intermediate vegetative form that is phenotypically arrested between a yeast and hyphal form. Budding from muriform cells in human tissue has been occasionally reported. The fungi that cause chromoblastomycosis have been found in soil and as airborne molds in Thailand but we could not find any published case reports of this disease.

Subcutaneous Zygomycosis

This disease is due to soil fungi found in leaf detritus and in the intestinal tract of amphibians. The commonest etiologic agents is Basidiobolus haptosporus. The disease is characterized by the development of massive, palpable, indurated, non-ulcerating subcutaneous masses on the limbs, trunk, chest, back or buttocks. The disease is chronic and develops slowly. Although it is seldom life threatening, it is very disfiguring. In Thailand, one case was reported in a 61 year old Chinese. Symptoms began with pain at the right heel. A month later, a hard non-tender mass appeared on the right calf. The biopsy of the mass showed diffuse inflammation with hemorrhage and necrosis. Large branching non-septate hyphae were abundantly present surrounded by eosinophils. Fragments of fungal elements were also seen in the cytoplasm of giant cells. The culture of tissue grew Basidiobolus (meristosporus) haptosporus. The disposition of patient was not mentioned in the report.

Rhinopsporidiosis

The disease is caused by an unclassified and unisolated organism known as Rhinosporidium seeberi. It causes a chronic granulomatous infection characterized by large polyps or tumors which are highly vascularized, friable and sessile or pedunculated. The commonest sites are the nose and conjunctiva. Uncommon sites are the pharynx, larynx, anus, vagina, ears and penis. The disease is chronic and usually has a long history without pain. Although the disease is benign, a few cases of generalized and fatal rhinosporidiosis are known. The diagnosis is confirmed by the histopathological finding of very vascular, fibromyxomatous connective tissue in which large, endosporulating spherules are found in various stages of development. Early stage spherules have a granular cytoplasm and a prominent nucleolus. The mature spherule contains endospores which stain with PAS and GMS. Occasionally spherules with broken walls and released endospores are seen. Treatment is by excision and electric cauterization. Recurrence following excision may occur.

In Thailand, the first three cases of rhinosporidiosis were reported in 1939, the fourth case was reported in 1980.

SYSTHEMIC MYCOSES

Histoplasmosis

Histoplasmosis is worldwide in its distribution. In the United States it is estimated that there are 200,000 new infections every year. However the reported prevalence of this disease in Thailand and the Far East is rather low. Histoplasmosis is the most recognized systemic fungal infection in Thailand. A survey of histoplasmin reactors was initially conducted in 1953-1955 among 329 student nurses who came from various parts of the country. Four per cent were found to be positive. The majority of the reactors came from the southern part of Thailand. In 1961, the first case of histoplasmosis was reported in a 16 year old boy who presented symptoms with generalized lymphadenopathy. The diagnosis was confirmed by both cultural studies and by animal inoculation. From 1966 to 1968, an extensive survey of histoplasmin reactors was conducted in Thailand (Figure 1). The number of positive reactors was low in the central region (3-9%), relatively high in the northern region (7-14%) and high (15-36%) in the Southeast and Southern region. A roentgenographic study of 236 histoplasmin reactors in Rayong showed that 25 per cent of them had calcifications, and fibrotic parenchyma of infiltration. However, since the rate of tuberculin skin reactors was as high as 90 per cent, differentiation between histoplasmonic lesions and tuberculotic lesions was not possible.

In spite of the high prevalence of population exposure to Histoplasma capsulatum var capsulatum, as indicated by the histoplasmin skin test reactions, no study has reported the successful isolation of this fungus from the environment. Case reports of histoplasmosis from Thailand are rare. The last case we could find was a report from 1980, the 22nd case. Patients come from various parts of Thailand, as also
shown in Figure 1. In a search for cases not reported in the literature, sixteen more were found. Seven of these cases came from a series of 165 autopsy cases with fungal infection at Siriraj Hospital where the largest number of autopsies was performed.\textsuperscript{32} Five cases came from the laboratory records of Chulalongkorn Hospital\textsuperscript{33} and one case from Khon Kaen Hospital.\textsuperscript{34} Three cases of fatal disseminated histoplasmosis were diagnosed at Ramathibodi Hospital from the opening of the hospital in 1969 up to 1985.\textsuperscript{35} To date, the total of known cases of histoplasmosis in Thailand is 38.

The symptoms of histoplasmosis, as with any disease caused by a living organism, are the result of the host's reaction to the organism and its products. \textit{Histoplasma capsulatum} itself causes a self limiting disease in a healthy host. Due to age related factors or immune deficiencies of the host, systemic dissemination to multiple organs may lead to a fatal outcome. In brief, histoplasmosis may be benign in a normal host and serious in a compromised host. In its benign form, the infection may not give rise to symptoms or it may induce a transient infection with flu-like symptoms, including enlarged hilar and mediastinal lymph nodes, and pulmonary infiltration. The disease may subside without specific treatment. In patients with an immune deficiency, histoplasmosis may destabilize into a systemic infection with hepatosplenomegaly and generalized organ involvement that often leads to a fatal outcome. In some cases, the flu-like symptoms exacerbate into a pulmonary infection which may occur with infiltration, nodules, adenopathy, cavitating lesions and pleural effusion. The lesions may heal with calcifications which are often multiple. Single coin lesions do occur. All of the pulmonary pathology, seen by radiologic examination, mimics tuberculosis and melioidosis, an infection caused by \textit{Pseudomonas pseudomallei}, which is endemic in Thailand.\textsuperscript{36-38} Cutaneous and mucosal ulcers do occur in the fingers, pharynx and larynx. In patients with an immune deficiency caused by various primary diseases or from genetic abnormalities, who do not respond to the organism, there may be very vague symptoms such as fever and weight loss. The disease progresses rather rapidly and fatally. The diagnosis can only be made by examining the bone marrow or sometimes even peripheral blood smears which may show yeast-laden macrophages. The number of yeast cells in the macrophages may be so high that one mistakes them as the granular cytoplasm of the neutrophils or macrophages.

The common clinical features of histoplasmosis in Thailand are cutaneous and oropharyngeal ulcers. Cutaneous ulcers are found on the face and fingers. Ulcers of the oropharynx have been found on the palate, tongue, epiglottis, gums and lips.\textsuperscript{39-41} The ulcers have a wide base and a raised edge. Multiple ulcers have also been seen. Cases with pulmonary involvement have been reported.\textsuperscript{42} as have cases of asymptomatic histoplasmosis.\textsuperscript{43} Chronic progressive histoplasmosis with multiple organ involvement and signs of adrenal insufficiency has been diagnosed.\textsuperscript{44,45} A case of chronic progressive fatal histoplasmosis with hypercalcemia was seen at Ramathibodi Hospital in 1984.\textsuperscript{46} Fulminant and fatal histoplasmosis in a lymphoma patient was diagnosed in a middle aged woman.\textsuperscript{47} Prior to 1970, only scant information on compromised patients was recorded. The role of immune deficiency in fungal infection has become of wide interest only in the past 15 years. In a review of autopsy cases, Parichatikanond\textsuperscript{32} found that in 7 cases of histoplasmosis, four patients had carcinoma of the liver, two had infectious mononucleosis and one had a prosthetic valve replacement.
Cryptococcosis

Cryptococcosis, a disease caused by the yeast *Cryptococcus neoformans* is manifested as a cutaneous ulcer, pulmonary infection and most commonly meningitis. This fungus lives and flourishes in pigeon excreta which is the common source of human infection through inhalation of the air borne cells of this fungus. In Chiang Mai C. neoformans was also found in the excreta of doves. The virulence of the organism resides in its potential for encapsulation. The common serotypes found are A and D.

Primary cutaneous cryptococcosis is uncommon. The cutaneous and mucocutaneous forms of this disease are usually a manifestation of the disseminated form in a compromised host. Pulmonary infections may develop in any part of the lungs. Unilateral or bilateral, lobar or miliary infiltration can occur. Healing without any residual effect may occur with or without calcification. Dissemination to the central nervous system may occur, depending upon the health of the host and the dose of infectious blastoconidia inhaled. Cryptococcosis of the central nervous system is usually manifested as a meningitis. Meningoencephalitis and cryptococcoma seldom occur. Cryptococcosis of the visceral organs and bones is usually the result of dissemination. Treatment failure with currently available antifungal agents is still as high as 25 per cent.

In Thailand, the first case was reported in 1960 in a 47 year old Thai woman who died from meningitis. At autopsy, encapsulated yeast cells were seen in the central nervous system (CNS) but confirmatory culture was not made. During the next 12 years after the first reported case, at least 22 other cases were reported in the Thai literature. About 70 per cent of these were infections of the CNS. Pulmonary infection was the next most common clinical form. In a series of 21 cases diagnosed at autopsy and including two previously reported cases, primary cryptococcosis was encountered in about 20 per cent. The rest of the cases were secondary infections in compromised hosts with the following diseases: carcinoma of the liver, cirrhosis of the liver, systemic lupus erythematosus, Hodgkin’s disease, leukemia, histiocytosis, aplastic anemia, haemolytic anemia and leprosy. Dual infections of cryptococcosis with other mycoses, such as aspergillosis, have been diagnosed. In general, the number of cases of cryptococcosis seen at the medical schools average 3-10 per year. This incidence depends on the number of patients seen at each hospital. Treatment failure is very high with the persistence of the yeast in the CSF in spite of adequate therapy and no known strain resistance to amphotericin B or 5 fluorocytosine. The mortality rate is 70-80 per cent.

Candidiasis

Candidiasis in a primary or secondary infection caused by members of the genus Candida. The most important species of Candida that causes disease is *C. albicans*. The common manifestations are mucocutaneous disease, oral candidiasis (thrush), vaginitis, pulmonary candidiasis, and candidiasis of the gastrointestinal tract with involvement of the esophagus and intestine. As is true for other fungal infections, the role of *C. albicans* in human health has changed. Systemic candidiasis due to other species of Candida has become a more frequent problem.

In Thailand, except for the medical schools, the microbiology laboratories that provide medical mycologic services still pay attention only to *C. albicans*. Few attempts are made to identify yeast isolates which do not produce germ tubes or chalmydosporidia. In the microbiology laboratory of Ramathibodi Hospital, where the annual number of diagnostic specimens gradually rose from 35,000 in 1970 to 55,000 in 1985, the number of yeasts isolated has also risen from 300 strains to 600 strains in the same period. This is about 0.8-1.0 per cent of the specimens submitted for microbiological examination. Among the yeasts identified, 40-60 per cent were *C. albicans*. Considering *C. albicans* and *C. tropicalis*, respectively, these species were commonly found in the following systems: respiratory 32 and 12 per cent, alimentary tract 8 and 1.4 per cent, urinary tract 9 and 2 per cent, blood 5 and 0.7 per cent. Other species of *Candida* found in descending frequency were *C. guilliermondii*, *C. krusei*, *C. parapsilosis* and *C. pseudotropicalis*. Amongst the few other yeasts found were *Torrulopsis glabrata* and Rhodotorula spp. Table 1). Data from Chiang Mai hospital also indicated that *C. albicans* was the most common yeast found (70%). *Candida tropicalis* was isolated 15 per cent and *C. parapsilosis* 9 per cent. The common systems involved were somewhat different from those observed in Ramathibodi Hospital. The prevalence of *C. albicans* and *C. tropicalis* found in various sites of the body were; genital tract 34 and 3 per cent, urinary tract 13 and 6 per cent, pus 11 and 3 per cent, body fluids 7 and 1 per cent, blood 1.6 and 1.3 per cent, mucous membrane 3.2 and 0.5 per cent.

In a review of 36 cases of candidiasis seen at Ramathibodi Hospital in 1969-1974, the mortality rate was as high as 28 per cent. Twenty five cases (69%) were fungemic of which 14 had received intravenous fluid therapy with a catheter and 3 had received hyperalimentation. The rest of the patients suffered fungemia following surgery. Four patients (11%) had pulmonary infections, two of which were community acquired. Three of them died. Two pa-
Table 1 Percentage of Candida Isolated at Ramathibodi Hospital 1970 – 1985

<table>
<thead>
<tr>
<th>Organisms</th>
<th>R-T</th>
<th>U-T</th>
<th>G-T</th>
<th>BL, Bm</th>
<th>A-T</th>
<th>CN</th>
<th>Misc</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>32.30</td>
<td>8.57</td>
<td>2.12</td>
<td>3.12</td>
<td>7.90</td>
<td>0.68</td>
<td>9.94</td>
<td>64.64</td>
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<tr>
<td>Cadida kru sei</td>
<td>1.14</td>
<td>0.24</td>
<td>–</td>
<td>–</td>
<td>0.24</td>
<td>–</td>
<td>0.12</td>
<td>1.74</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>1.14</td>
<td>0.12</td>
<td>1.12</td>
<td>–</td>
<td>–</td>
<td>0.24</td>
<td>0.12</td>
<td>2.74</td>
</tr>
<tr>
<td>Cadida quilliermondii</td>
<td>0.81</td>
<td>1.14</td>
<td>0.24</td>
<td>0.24</td>
<td>0.24</td>
<td>0.45</td>
<td>0.68</td>
<td>3.80</td>
</tr>
<tr>
<td>Cadida tropicalis</td>
<td>12.1</td>
<td>2.18</td>
<td>0.12</td>
<td>0.68</td>
<td>1.48</td>
<td>0.12</td>
<td>4.34</td>
<td>21.02</td>
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<td>Geotrichum Candida</td>
<td>0.35</td>
<td>0.35</td>
<td>0.12</td>
<td>0.12</td>
<td>0.35</td>
<td>1.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhodotorula sp.</td>
<td>0.24</td>
<td>0.12</td>
<td>0.12</td>
<td>–</td>
<td>0.24</td>
<td>–</td>
<td>0.12</td>
<td>0.60</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>–</td>
<td>0.12</td>
<td>–</td>
<td>0.24</td>
<td>–</td>
<td>1.72</td>
<td>0.12</td>
<td>2.20</td>
</tr>
<tr>
<td>Torulopsis glabrata</td>
<td>0.58</td>
<td>0.80</td>
<td>–</td>
<td>0.12</td>
<td>–</td>
<td>0.12</td>
<td>0.35</td>
<td>1.97</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>48.67</strong></td>
<td><strong>13.64</strong></td>
<td><strong>3.72</strong></td>
<td><strong>4.52</strong></td>
<td><strong>9.86</strong></td>
<td><strong>3.45</strong></td>
<td><strong>16.14</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

*R-T = Respiratory tract, U-T = Urinary tract, G-T = Genital tract, BL = Blood, BM = Bone Marrow, A-T = Alimentary tract, CN = Central nervous system, Misc = Miscellaneous

Patients had primary meningitis of whom only one survived. Five fatal cases were found to have involvement of the following organs: esophagus (1 case), stomach (2 cases) and duodenum (2 cases). One case had myocarditis complicated by pneumonia. Thirty of them had predisposing factors as follows: bacterial infection with prolonged antibiotic therapy (44%), broken mechanical barriers as a result of retained intravenous or urinary catheters (64%), and surgery (42%). Only two patients were leukemic. The rest were patients with various other disorders. The main site of isolation of the etiologic agents was the blood. Only two cases had funguria and only patients with meningitis had the organism in the spinal fluid. A striking feature was the high percentage of isolation of C. guilliermondii (36%). In only 19 per cent of the cases was C. albicans isolated. The other Candida species isolated were C. kru sei and C. parapsilosis.

Penicillosis marneffei

Species of the genus Penicillium are distributed worldwide in the human environment. However, systemic infections caused by Penicillium spp. are uncommon. In Thailand, the only known species of Penicillium which causes serious systemic infection is P. marneffei. It is the only species of Penicillium which is dimorphic and is known to be pathogenic to animals and man. It was first isolated from bamboo rats in Viet Nam in 1956. Its human pathogenicity was reported in a laboratory acquired infection three years later. In 1973 the first case of natural human infection was reported by diSalvo et al. In Thailand, to date, there have been eight known cases of penicillosis marneffei. The first case was found in 1974 in a 6 year old girl with malnutrition. The first series of 5 cases from Thailand was reported in 1984. The common clinical manifestations were chronically ill with fever, enlargement of the lymph glands, liver and spleen, and cutaneous manifestation as nodular eruptions. Multiple abscesses were found in three cases. Osteolytic lesions of the flat and long bone were seen in two cases. In 1984, the sixth and fatal case of disseminated penicillosis marneffei was seen at Siriraj Hospital in a 45 year old man who came from Petchaboon. Two more cases are known: one fatal case from Songkla and one female resident of Kanchanaburi who was successfully treated at a private hospital in Bangkok. Six of them were in compromised hosts, i.e., tuberculosis (2 cases), systemic lupus erythematosus, lymphoproliferative disorder, malignant histocytosis and malnutrition. No history of compromising conditions was found in the other two patients. It can be seen that these patients came from different parts of Thailand, and the true geographic distribution of P. marneffei in Thailand is currently unknown. (Figure 2) Eight fatal cases of penicillosis marneffei were reported from the Peoples Republic of China in 1985. One case reported from Hong Kong in a 54 year old Chinese sailor had presented unsolved lobar pneumonia, cervical lymphadenopathy, generalized subcutaneous abscesses and pericardial effusion. P. marneffei was isolated from his pericardial fluid and subcutaneous pus. The tissue form cells of this species were demonstrated in histological sections of lymph nodes and lung tissue. The patient was cured but he had a persistent depression of T. lymphocyte function and many episodes of opportunistic infection. The cause of his immunodeficiency was undetermined. All reported cases for this disease occurred in residents of Southeast Asia and mainland China. The only case of pulmonary infection by P. marneffei in America was reported by...
Pauller et al. However, the patient had a history of travel in Asia. Thus far, it appears that penicillosis marneffei is a fatal systemic mycosis which is endemic to Southeast Asia, Hong Kong and the Peoples Republic of China.

**EMERGING MYCOSES**

In the last decade there have been several fungi of previously unknown human significance that have been established as agents of human disease. More and more such genera and species are being described in the literature. Among them are fungi previously involved in animal and plant disease. One large group of fungi that causes these emerging human diseases is made up of dematiaceous hyphomycetous fungi (black molds). Ajello et al. first introduced the term phaeohyphomycosis to cover all these mycoses, mainly opportunistic mycoses, which are due to a variety of dematiaceous fungi. In addition to the already large group of known fungi causing phaeohyphomycosis, there will be more and more emerging human diseases caused by other obscure fungi.

**Phaeohyphomycosis**

In 1974 Ajello et al. proposed the term phaeohyphomycosis to replaced the term phaosphorotrichosis which Mariat et al. had coined to describe the cutaneous and subcutaneous abscesses caused by dematiaceous fungi. In tissue these fungi developed hyphae and thick and thin walled cells with partitions in one plane. In 1977, Ajello expanded the definition of phaeohyphomycosis to cover various opportunistic infections caused by dematiaceous fungi. These appear in tissue as hyphae with thick walled chlamydospore like cells. Many mycoses of this form have been confusingly described in the past as subcutaneous and cerebral chromoblastomycosis, subcutaneous and cerebral chromomycosis, cladosporiosis, phaeosphorotrichosis, phaeomycotic cysts or abscesses or simply, in many instances, as granulomas. In 1981 Ajello reviewed the causative agents of phaeohyphomycosis and listed 32 species classified in 18 genera. Since them more agents have been described, giving a total of 71 species classified in 39 genera. These fungi are also known to cause disease in birds, cats, dogs, fish, toads and horses. The most common agents are Exophiala jeanselmei, Wangiella dermatitidis, Xylohypha (Cladosporium) bantiana and Curvularia lunata. Based on the level of host involvement, four basic forms of phaeohyphomycosis can be distinguished, i.e. superficial, cutaneous and corneal, subcutaneous, and systemic. The high risk group is compromised patients and healthy people with repeated injuries, soil exposure or surgery. Injury may escape recognition as in the case of keratitis and subcutaneous cysts. Endocarditis and osteomyelitis following surgical correction of ventricular septal defects should also be noted.

In the Thai literature, phaeohyphomycosis has been described under various names such as phymycosis and subcutaneous cystic granuloma. The lesions reported usually appeared on the foot, ankle, heel, leg, elbow, the anterior clavicular area and the temporal region. The diagnosis were mainly by histopathology. One of the agents reported was Exophiala jeanselmei (Gougerotii). From a series of cases reported by Chantarakul, six were seen in 1968-1969 and surprisingly, four of them came from Nakom-Pathom, a province near Bangkok. In 1984, a fatal case of cerebral phaeophyphomycosis in a 25 year old woman with beta-thalassemia hemoglobin E disease and autoimmune hemolytic anemia was seen at Ramathibodi Hospital. The patient presented signs of increased intracranial pressure. The computerized tomographic (CT) scan revealed multiple abscess, from which pus was aspirated at surgery and revealed brownish septate hyphae. Culture of pus
grew *Xylohypha bantiana* (*Cladosporium trichoides*). The preliminary diagnosis of the patient was cerebral chromomycosis. Treatment with fluorocytosine and ketoconazole was given for three months without signs of improvement as confirmed by CT scan. A second attempt at surgical removal of the abscess was performed without success. The patient died five months after the diagnosis had been made.

**Pythiosis insidiosii**

Pythiosis insidiosii is primarily an oomycete disease of horses, cattle and dogs caused by the aquatic mold *Pythium insidiosum* which belongs to the Phylum Oomycota, Order Peronosporales.\(^{75-77}\) Currently there is no publication of human infection caused by this water mold that can be cited from the English literature. During the year 1984-1985, two cases of a subcutaneous mycosis caused by *P. insidiosum* (confirmed by Ajello, L.), were seen at Siriraj Hospital.\(^{78}\) They were both male patients, aged around 30 years and both had thalassemia as their underlying disease. Their lesions occurred in the arm in one case and in the thigh in the second case. There was no history of trauma, but both of the patients had worked in mud 5-6 months prior to the onset of their disease. There was no response to therapy with ketoconazole and clotrimazole. Both patients, however, responded to therapy with saturated potassium iodide solution. Clinical improvement occurred 3 weeks after initiation of therapy and their clinical signs disappeared in three months. Therapy was continued for a total course of 6 months. No relapse was seen in both cases when the patients were followed up one year later.

During the year 1986, four patients (2 males and 2 females with ages ranging from 19-36 years) were admitted to Ramathibodi Hospital with arterial occlusion of the lower limbs. All of them were farmers from the north, northeast and central parts of Thailand. All of them had thalassemia hemoglobinopathy syndrome. The primary site of infection was established in only one case. It began with a painful nodule at the ankle. No definite history of trauma could be obtained, except for one patient whose calf had suffered a minor burn from a motor cycle exhaust pipe. The symptoms that brought all 4 patients to the hospital were those of subacute to chronic arterial occlusion of the lower limbs. Signs of gangrene were present on admission in one case. The infection spread rapidly via the medium sized arteries of the lower limbs with evidence of crossing to the arteries of the opposite limb in two cases. Aneurysm of the iliac artery occurred in two cases. Amputations of the lower limbs failed in two fatal cases. These patients had endured their disease for only 11 an 16 months respectively. The histopathology of the 4 cases was basically that of a suppurative and granulomatous inflammation of the medium sized arteries, and adjacent soft tissue. Involvement of the metatarsal joint was seen in one case. Broad, rarely septate hyphae were present in the lesions. Occasional branching at right angles was seen. A water mold was isolated from the thrombi and soft tissues in three of the cases. This oomycete was cold sensitive and easily lost viability both in tissue and in culture following exposure to refrigerator temperatures. Only two isolates among the three were available for identification and were confirmed by Ajello, L (Centers for Disease Control, Atlanta, Georgia) to be *P. insidiosum*. The cell walls of the aquatic molds contain cellulose, and their cell membranes lack ergosterol which is present in the mycelium of true fungi.\(^{79}\) Thus it was found ineffective in the treatment of the oomycete infections caused by *P. insidiosum*. The only therapy presently available is surgery and oral medication with saturated potassium iodide.\(^{76,78}\)

**CONCLUSION**

It is clear that Thailand is a country with a high incidence and prevalence of mycoses. The true number of cases of fungal infections is much greater than that diagnosed and reported in the literature. Statistics on the incidence, morbidity and distribution of mycoses are limited by several factors. The most basic, but very important limitation is the scarcity of people trained in medical mycology. Hence, there is ignorance and under diagnosis and under reporting of the diseases. Fungal infections are not notifiable diseases and data are therefore only collected by a few interested individuals.

The problems associated with the mycoses are neither acute nor initially life threatening, but there is a high risk of leaving patients to develop a potentially fatal infection. The chronicity and the resistance to therapy of many mycoses result in an economic burden for the individual and society as a whole. These facts should be a point of concern to anyone who deals with the medical care of patients and the well being of humans. It should also be realized that the problems associated with the mycoses are by no means unique or static. At any time, a single problem in the area of mycology may be solved, but more than a decade has passed since Ajello\(^{66}\) likened mycoses to an iceberg with "its vast bulk... submerged in a murky sea of ignorance". Fresh problems remain in plentiful supply.

In Thailand not only does the underdiagnosis of known human mycoses remain a problem, but also the emergency of mycoses caused by previously unsuspected saprophytes with a pathogenic potential.
Such cases are certainly coming into the hands of physicians. There is no doubt that throughout the field of medical mycology, there is a constant and necessary interplay between diagnosis and management. Treatment cannot be initiated properly without a diagnosis. The increasing ability to diagnose fungal infections is obviously the basic goal on which necessary interplay between diagnosis and management of mycological diseases depends.

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