Medical Mycology in the Orient: Where Are We Going?

Glenn S. Bulmer

Department of Laboratory Medicine, University of Santo Tomas School of Medicine & Surgery, Manila, Philippines

=Abstract=

Medical mycology has gone through five distinct eras: 1) Fungi causing dermatophytoses, 2) Discovery of rare and fatal systemic mycoses, 3) Realization that fungi cause common and subclinical diseases, 4) AIDS and the era of the compromised host, 5) Broad-spectrum antifungals with few side effects.

I think that most would agree that the developed countries are in stages 4 & 5. But which one of these eras are we in now in the Orient? From my 35 years experience of working and living here I believe we still live in all of these eras. In developing countries we have a few very advanced medical centers that are on the cutting edge of technology. But, what about the rural and poorer sections of our countries? The places where modern medicine is not available at a price our citizens can afford. Are we by passing these areas in our excitement to join the biotechnology race in the world? I know that in many places this is true. National pride can cover national shame.

For the remaining time I will discuss some of the diseases that we should be looking at from a different perspective. What is needed in these areas of our countries? How can we approach these problems so that all our citizens gain from our advanced technology? How can we use the modern high technology advances in medicine to the best advantage of all our people? It is very difficult to know where we are going until we know from where we came.

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INTRODUCTION

To paraphrase Kung Fu Tzu (Confu cius), 'It is difficult to know where we're going unless we know where we came from'. With this in mind, I would like to discuss what I perceive as the five historical eras through which medical mycology has evolved. I will discuss these briefly and then attempt to relate them to the present and future status of this medical discipline in your country.

ERAS IN MEDICAL MYCOLOGY

Era # 1. Fungi causing dermatophytoses

These diseases hold the spotlight in the study of infectious diseases because the first microorganism ever cultured from a human case was a dermatophyte in the year 1839. You will note, that this was decades before etiologic agents of tuberculosis and all bacterial diseases were grown in the laboratory. At that time, two groups of scientists became interested in the dermatophytoses, namely the botanists and the practicing physicians. As one can

†Corresponding author: Glenn S. Bulmer, 68 Beverly Hills Ave., Beverly Hills Subd., Taytay, Rizal, 1920, Philippines
E-mail: glenn@compass.com.ph

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imagine, the botanists were solely interested in the fungi as plants. Thus, the etiologic agents of dermatophytoses were all named using the classical binomial nomenclature (eg. *Trichophyton rubrum*) with utter disregard to the human disease. On the other hand, the physicians cared little about etiologic agents and how the botanist had named them. Thus, he used the descriptive medical terminology for these diseases. Since the lesions appeared to be caused by a worm, the physician coined the term Tinea, which is the Latin genus for worms. He then added a second term which described the primary location of the lesion on the patient, eg., corporis, pedis, capitis, etc. Thus, from the very beginning, we had two groups of scientists using totally different systems of nomenclature. Unfortunately, to this day, these two systems still exist in the study of dermatophytoses. In many regards they have impeded progress in this field.

Despite the divisions within this field, this historical perspective demonstrates clearly that the physicians interested in skin diseases (what we would call today, the dermatologists) were the very first medical people to study fungus diseases in humans. Even to this day, no matter what country I visit, it is apparent that the dermatologists have always been the historical leaders in the field of medical mycology in their country. This is even true to this day although in the decade of the 90's, the infectious disease physicians have become increasingly aware of the other mycoses.

Era # 2. Discovery of rare and fatal systemic mycoses

During this era, all of the major systemic mycoses were described with corresponding etiologic agents. However, it must be recognized, that during this era, the systemic mycoses were accepted to be rare and in all cases, fatal. Examples of diseases discovered in this era include: Candidiasis (disseminated form) 1890; Blastomycosis 1894; Cryptococcosis 1894; Aspergillosis 1856; Coccidioidomycosis 1891; Histoplasmosis 1904; Paracoccidioidomycosis 1908; Sporotrichosis 1900. During this era, we learned much about the ecology of

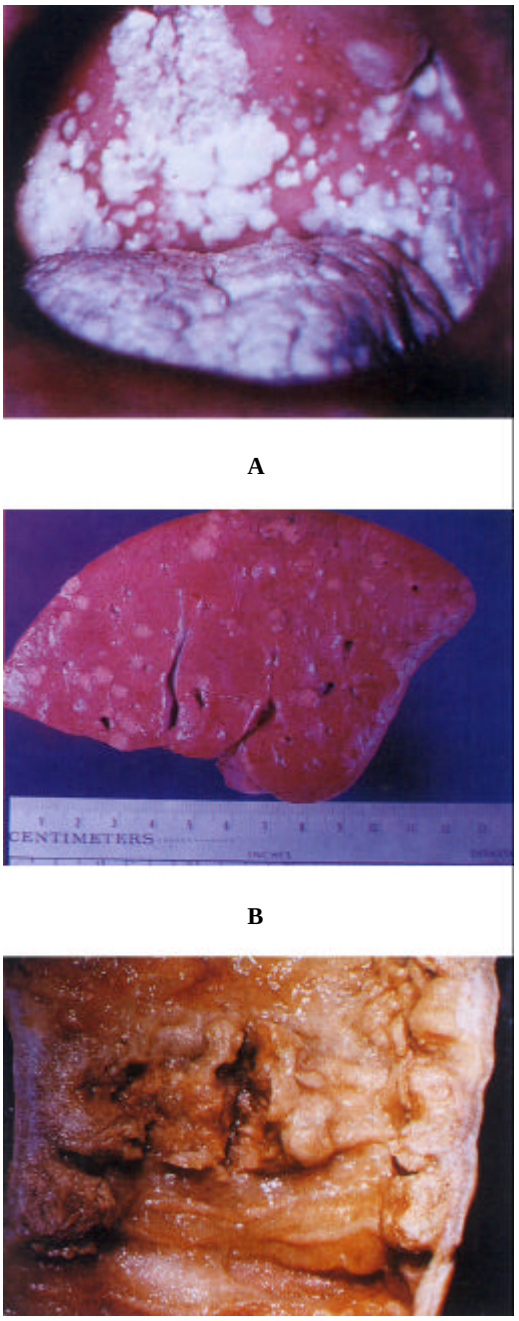

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Fig. 1. Candidiasis. **A.** Oral thrush. White patches of pure *Candida albicans* on tongue and oral cavity. **B.** Liver from cancer patient who died of disseminated candidiasis. White patches are pure *Candida* sp. **C.** Section of gut (ileum) from cancer patient who died of disseminated candidiasis. A *Candida* sp. which has caused massive gut erosions.

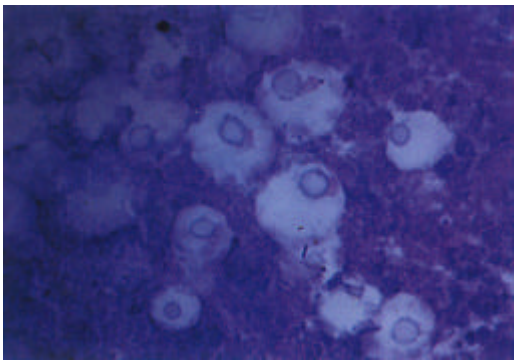


Fig. 2. Cryptococcosis: PAS stain of tissue from patient with cryptococcosis. Note the yeast cells surrounded by large, clear areas: this is the capsule which inhibits phagocytosis, ie., it is a virulence factor.

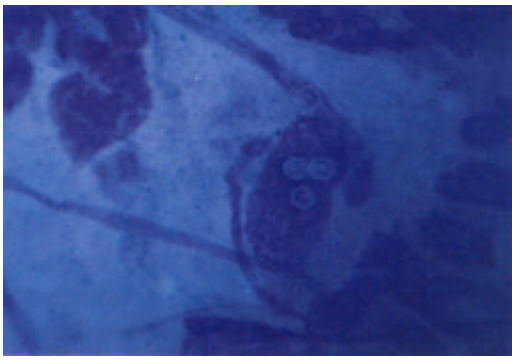
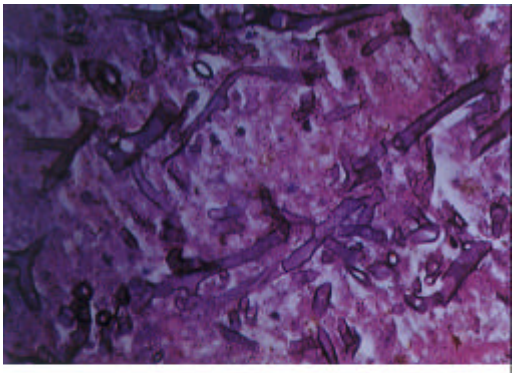


Fig. 3. Histoplasmosis: Wrights (or Giemsa) stain of tissue from a patient with histoplasmosis. Note the 3~4 intracellular yeast cells which are ovoid and 3~4 microns in diameter.



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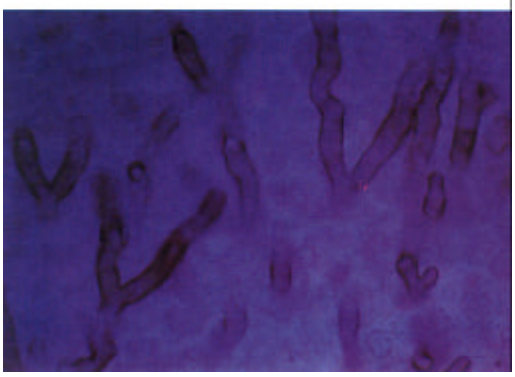

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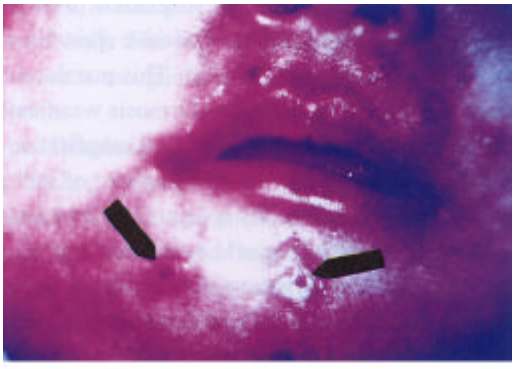
Fig. 4. Aspergillosis/Phycomycosis. **A.** PAS stain from a patient with aspergillosis. The key diagnostic features are the size of the hyphae (5~6 micra in diameter) and the dichotomous branching (45 degrees) of the hyphae. **B.** Phycomycosis (mucormycosis). The hyphae is larger (up to 10 micra) than in aspergillosis, lacks cross walls and does not exhibit dichotomous branching.



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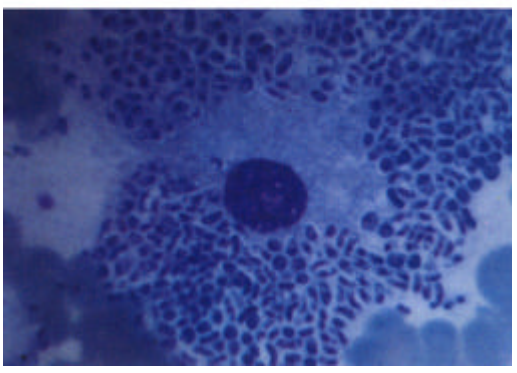

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Fig. 5. Penicilliosis. **A.** Face of child with penicilliosis. Note characteristic "target" lesions (see arrows). **B.** Smear from patient with penicilliosis. This organism is an intracellular parasite. In this disease the fungus (*Penicillium marneffei*) is a slightly elongated yeast (3 x 8 micra) in vivo, and divides by division (fission).

the etiologic agents, histopathology of the diseases and culture and identification of the fungi. However, these diseases were still considered to be rare and uniformly fatal, during this era until the 1930's.

Era # 3. Realization that fungi cause common and subclinical diseases

When the Americans finally entered World War II (1941), they recruited thousands of citizens into the Armed Forces. As part of this process, all were given medical examinations which included X-ray and skin testing for tuberculosis (the Americans have never used BCG prophylactically and thus, a positive TB skin test indicated past exposures to the bacillus). This resulted in the observation that thousands upon thousands of Americans (mostly from eastern United States) had positive chest films but were negative to tuberculin. This puzzle resulted in the finding that histoplasmosis was (and still is today) the major cause of lung calcification in the US. Fortunately, the vast majority of individuals never had clinically apparent histoplasmosis. This awakened the world to the fact that histoplasmosis can be an extremely common mycosis in certain endemic areas and most to these are classified as having subclinical histoplasmosis.

About the same time, another disease fungus was been recognized in South Western United States. This disease was called coccidioidomycosis and upon initial discovery, it almost resulted in the closure of Edward Air Force Base (where you have often seen on TV, American astronauts landing from a space shuttle mission). This disease, like histoplasmosis occurs in millions of Americans in a subclinical form. These are two examples of systemic mycoses that awakened the world to the realization that some of the mycosis may be very common, existing in subclinical forms.

Era # 4. AIDS and the era of the compromised host

If you want to thank the disease AIDS for anything, we probably should give it credit for ushering in the era of the compromised host. As we all know approximately 90% of all AIDS patients have fungus diseases. This event, which was only realized in the 1980's, opened the eyes of medical personnel all over the world to the fact that all immuno-compromised patients were the primary target for many frequently fatal, systemic mycoses. This included patients with cancer, lupus, diabetes, transplants, surgery and in fact, in a broader sense, all individuals admitted to a hospital are immunocompromised. Thus the era of the compromised host has propelled the mycoses to center stage, next in importance to the bacterial and viral diseases.

Era # 5. Broad spectrum antifungals with few side effects

As if in response to the dawning of the era of the compromised host, new broad spectrum antifungal agents with nominal side effects began to appear in the market. The two most outstanding of these agents is fluconazole (Diflucan®) marketed by Pfizer Pharmaceuticals and itraconazole (Sporanox®) marketed by Janssen Pharmaceuticals (a division of Johnson & Johnson). These two agents found worldwide recognition for their effectiveness against most of the mycoses, ease of administration and virtually lack of toxicity. Thus for the first time in the history of medical mycology, it was now possible to treat most of the mycoses successfully. From a personal point of view, it is difficult for me to tell you how refreshing it became to not only diagnose a fungus disease but in many cases, for the first time ever, to treat these patients successfully. I have taught medical mycology for over 40 years, but it has only been during the past decade that I have seen cures in many patients with mycoses.

Now let's look back at these 5 eras of the evolution of medical mycology and decide where we stand today. If we're talking about advanced countries such as USA, Australia and many countries in Europe, it is an easy matter to realize that these countries have gone through all of these major eras and are now entering the next potential era called Molecular Biology. However, not all countries in the world are in such advanced stages of development, thus the basic question has become far more

complex especially for us living in Asia. But it is a serious question that all of us must face if we wish to honestly address the health needs of all the people in your country. I know that in several of our countries in Asia, there are some truly outstanding, advanced medical centers in such cities as Seoul, Beijing, Shanghai, Manila, etc. Such centers give us pride and, we like to think we are close to attaining the status of similar centers in advanced countries. But, let's be honest, the number of these advanced medical centers throughout all of Asia is extremely small, and from my experience, they only serve the wealthy and elite of a country or region. In my opinion we need to be looking more at the health care facilities available for the remaining 95% of our citizens. You are the ones who should be looking at this for your country. This is not something that can be done by outsiders such as myself.

Another aspect that concerns me is my perception that many countries use medicine and science to promote the nation's worldwide esteem and prestige. The best current example is PCR technology. This type of science is extremely expensive and as far as I have seen today, it has yielded nothing of any practical diagnostic value for us in mycology. When I used the terms "practical diagnostic value" I am referring to diagnostic technologies that 90% of our citizens can afford. Thus it appears to me that the major reason for such high level funding of advanced technologies, such as PCR, is to promote the prestige of the country in the international arena. Does this mean that funding for such advanced technologies should be minimized in developing countries? My answer to that is YES. It should be reduced or eliminated so that funding can be directed towards practical and affordable medical solutions for the average citizens of our countries. In my opinion, let the wealthy countries of the world develop the advanced technologies and when they reach a point where they are financially feasible for all of our citizens, then we should fund mechanisms through which we can "transfer" these technologies to medical centers all over our countries.

IMPORTANT MYCOSES IN THE ORIENT

For the remaining time, I would like to mention a few of the important mycoses that we are seeing in the Orient and suggest areas that I feel need to be investigated. As suggested above, I am only emphasizing problem areas that I feel can be approached with the goal of developing solutions that are economically feasible for our citizenry in the immediate future.

A. Candidiasis

This is the most common mycosis in the world today. It is endogenous in origin and therefore, is worldwide. The key to the management of this disease is recognition and control of predisposing factors.

a. Diagnosis. This is still the greatest problem in dealing with candidiasis. Many serologic tools have been tried but I know of none that are of commercial value in the Orient. Desperately needed are newer and cheaper methods of diagnosis, eg., look how the simple and inexpensive the germ tube assay method has swept the world for the identification of *Candida albicans*.

b. Fungemia. Advanced countries have several excellent cultural procedures to assay for fungemia (especially, candidemia). Unfortunately, these are too expensive for us because they must be imported from advanced countries. What we need is a simple and inexpensive method of assay, eg., drawing blood, lysis of cells, spinning the fungus (yeast) to the bottom of a centrifuge tube, pouring off the supernatant and culturing the pellet.

c. Cheaper therapy. All of the newer therapeutic agents are modern medical miracles. But, they are too expensive for the vast majority of our citizens. Why can't we investigate some of our age old medical agents (i.e., traditional) to determine if they have practical and ethical significance?

d. Immunology. In some regards, this area of research is expensive to fund but if we could find some way to overcome T-cells defects, we might

Fig. 6. Keratomycosis: Eye of patient with keratomycosis (mycotic keratitis). If untreated the patient will go blind. This is an agricultural worker who implanted fungal spores during slight abrasion to the eye, while working in the fields.

be able to save the patient a lot of therapeutic and hospitalization expenses.

e. Mechanisms of disease. To this day we don't know why or how these yeasts cause disease. Is this related to pseudohyphal formation or other virulence factors?

f. Vaccine. Is there any potential for the development of a vaccine for patients that are predisposed to disseminated candidiasis? Frankly, I'm not too optimistic about the development of a vaccine against normal flora. However, more than once I have been pleasantly surprised. Currently much American research is in this direction.

B. Cryptococcosis

This is caused by a yeast that enters humans through the lungs. It finds its way to the meningeal area of the brain and is fatal if untreated early enough. The disease is worldwide in distribution and accounts for the death of >20% of AIDS patients in many areas of the world. The organisms are associated with pigeon droppings and in the soil around certain trees, especially the Eucalypti (in topical regions). It is easy to diagnose (India ink preparation or latex agglutination test of the CSF): any patient with a persistent headache should be investigated.

a. Where is the etiologic agent of this fungus found in nature in Korea? With available selective and differential media this is not difficult or expensive to investigate.

b. The biggest current problem with cryptococcosis is one of education. Few physicians are aware of this disease and how to diagnose and treat it. This is a matter or increasing awareness to this disease within the profession.

c. Why are so many cases of cryptococcosis found in individuals with depressed T-cell responses? What role does this play in pathogenesis?

C. Histoplasmosis

This is a granulomatous disease of the lungs that is a perfect mimic of TB. Over 70 million people in the USA are skin test positive to it. It is a worldwide disease that is associated with the droppings of certain black birds, chickens and bats.

a. How much histoplasmosis is in Korea? Is it being misdiagnosed as TB (as happened in the USA)? Do all of the drug resistant cases of TB really have TB--or were they misdiagnosed and are now being treated incorrectly?

b. Where is the etiologic agent found in nature in Korea and what % of the population is skin test positive?

c. Is a vaccine possible and feasible for endemic areas? Considering the serology of this disease it seems that one could be possible.

d. What is needed also are better and cheaper methods of therapy.

D. Aspergillosis / Phycomycosis (Mucormycosis)

These diseases are caused by fungi that are floating through the air everyplace in the world. The etiologic agents seem to love blood supplies in immuno-compromised patients. If untreated rapidly, most are fatal. Diagnosis and professional awareness are the biggest problems.

a. How can we control the spread of these pathogens better in hospital settings?

b. Is a vaccine feasible for susceptible hosts?

E. Penicilliosis

This is a new, fatal mycosis that appears to be

limited (so far) to more tropical areas in SE Asia and SW China (so far, not reported north of the Yangtze River). It is so new that we don't know: where the etiologic agent exits in nature; how the disease is spread; and what is the cause of death!

a. What is the distribution of this disease? Is it spreading to other areas in Asia?

b. Where does the etiologic agent exist in nature? What are the infectious particles and how and where does it enter potential hosts?

c. Can skin test material be made? Are vaccines possible for susceptible hosts?

d. Is there a link between this disease and histoplasmosis? They are so similar that in most regards I can't help but wonder if penicilliosis is another type of histoplasmosis (in fact, we already have 3 forms of histoplasmosis: var. *capsulatum*; var. *duboisii*; and var. *farciminosum* and Medical Mycology is full of diseases with more than one genera of fungi as etiologic agents).

F. Keratomycosis (mycotic keratitis)

This is a disease of eyes that is caused by over 70 species of fungi that are found in nature. It leads to blindness if not treated. In more tropical areas of Asia it is common amongst agricultural workers, especially those working in rice fields (so-called rice paddy disease).

a. Is this a problem in agricultural areas of Korea?

b. Laboratory diagnosis is not a major problem, so the problem is more related to physician awareness of diagnostic methods.

c. Are cheaper therapy methods available, eg., dilution (1:50) of the new liquid itraconazole (1 part) with ophthalmic solution (49 parts) has worked with us in a limited number of cases. Diluted this amount, it is still effective and very affordable to all (ie., it is cheap).

CONCLUSION

These are some of my ideas of what medical mycology problems should be addressed in your country today. However, I don't live here. I don't know where medical mycology stands today throughout all of Korea. This is for medically knowledgeable inhabitants like you to decide. Don't be swayed by expensive "glamorous" projects that are designed to put Korea on the world medical stage. Instead, look at your people (both north and south) and assess what they need and what they can afford.

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