Mycology newsletter

The ECMM/CEMM Mycology Newsletter is mailed to the members of the national societies affiliated to the European Confederation of Medical Mycology (about 3000 in 19 different countries)

0/97

ECMM
European Confederation of Medical Mycology
CEMM
Confédération Européenne de Mycology Médicale

Message from the President

The ECMM President is happy to take the opportunity of this first issue of the ECMM Newsletter to greet all ECMM members and their Mycological Societies and extend a cordial welcome to the Russian Society of Mycology which has recently joined our Confederation.

We had an excellent Congress in Lisboa and we do hope that such a meeting will boost the development of medical mycology in Portugal. During this meeting Dr. Maria Anna Viviani was elected by the Council to the position of General Secretary. I would like to express my warmest thanks to Dr. David Warnock, who had the difficult task of being the first General Secretary, for his considerable effort in setting up the Confederation from nothing.

We realized during the last Council meeting in Lisboa that communication was sometimes difficult or slow between delegates and their Societies and between the 19 Mycological Societies or Groups. For this reason we decided to publish a Newsletter with two issues per year mailed to all individual ECMM members. The General Secretary is in charge of editing the Newsletter. This method of communication is very important and I encourage everyone to participate in the venture by sending their comments or suggestions to Dr. Viviani. One of the purposes of the Newsletter is to activate the Working Groups which are a major goal of our Confederation. If you are interested in participating in these Working Groups please contact your national delegate.

We would like to have the first reports of these groups during a special Session at the next ECMM Congress which will be held in Glasgow on 11-13 May 1998 with Gillian Shankland as organizer. I thank warmly all delegates, Maria Anna Viviani and Lars Edebo, our Treasurer, for their efforts and their commitment to ECMM.

Bertrand Dupont

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Affiliated Societies

Associação Portuguesa de Micologia Médica (ASPOMM)
President: M. Rocha
Vicepresident: R.M. Velho
Secretary: M.L. Rosado *(ECMM delegate)*
Treasurer: M. Gardete
Membership 1996: 47
National meeting: May 1997, Lisboa
Newsletter

Asociacion Española de Micologia Seccion de Micologia Medica
President: J.M. Torres Rodriguez
Vicepresident: M.L. Abarca Salat
Secretary: S. Santamaria del Campo
Treasurer: A.J. Carrillo Muñoz
President Mycology Section: J. Ponton *(ECMM delegate)*
Membership 1996: 65
National meeting: 1998, Cadiz
Journal: Revista Iberoamericana de Micologia

British Society for Medical Mycology (BSMM)
President: E.G.V. Evans *(ECMM delegate)*
Secretary: D.W. Warnock
Treasurer: G.S. Shankland
Membership 1996: 260
National meeting: 11-13 May, 1998, Glasgow (joint with ECMM Congress)
Newsletter

Bulgarian Mycological Society (BMS)
President: T. Kantardjiev *(ECMM delegate)*
Membership 1996: 27

Czech Mycological Group
ECMM delegate: A. Tomsíková

Danish Society for Mycopathologia
President: E. Svejgaard
Secretary: M. Kieffer
Treasurer: J. Stenderup *(ECMM delegate)*
Membership 1996: 65

Deutschsprachige Mykologische Gesellschaft e.V. (DMykG)
President: H.Bernhardt *(ECMM delegate)*
Vicepresident: H. Chr. Korting
Secretary: C. Seebacher
Treasurer: W. Fegeler
Membership 1996: 1100
National meeting: September 18-21, 1997, Aachen

Federazione Italiana di Micopatologia Umana e Animale (FIMUA)
President: M.A. Viviani *(ECMM delegate)*
Vicepresident: S. Oliveri
Secretary: I.G. Dragoni
Treasurer: G. Morace
Membership 1996: 150
National meeting: Autumn 1998, Milano
Newsletter

Greek Mycological Group
ECMM delegate: O. Marcelou-Kinti

Hungarian Dermatological Society Mycology Section
President: I. Török *(ECMM delegate)*
Secretary: G. Fekete
Membership 1996: 25
National meeting: March 21, 1997, Budapest

Israel Society for Medical Mycology
President: E. Segal
Secretary: I. Berdicevsky *(ECMM delegate)*
Treasurer: D. Elad
Membership 1996: 80

Polish Dermatologic Society Mycology Section
President: E. Baran *(ECMM delegate)*
Vicepresident: P. Ratka
Secretary-Treasurer: M. Ziarkiewicz
Membership 1996: 98
National meeting: September 25-27, 1997, Zakopane-Koscielisko
Journal: Mykologia Lekarska (Medical Mycology)

Netherland Society for Human and Veterinary Mycology (NVMy)
President: R.G.F. Wintermans
Scientific Secretary: G.S. de Hoog *(ECMM delegate)*
Secretary: E.P.F. Yzerman
Treasurer: R.W. Brimicombe
Membership 1996: 110
National meeting: April 2, 1997, Lunteren

Russian Society of Mycology
President: S.A. Burova *(ECMM delegate)*
Vicepresident: V.B. Antonov
Secretary: N.M. Vasilyeva
Treasurer: I.V. Kurbatova
Membership 1996: 25

Société Belge de Mycologie Humaine et Animale / Belgische Vereniging Voor Menselijke en Dierlijke Mycologie
President: N. Nolard
Vicepresident: H. Vanden Bossche, M. Song
Secretary: D. Robbrecht, J. Boelaert
Treasurer: M.C. Lestienne
ECMM Delegate: D. Swinne
Membership 1996: 210
National meeting: April 19, 1997, Antwerp

Société Française de Mycologie Médicale
President: J.P. Seguela
Vicepresident: R. Grillot, C. de Bievre
Secretary: B. Dupont *(ECMM delegate)*
Treasurer: P. Boiron
Membership 1996: 360
National meeting: March 20-21, 1997, Arcachon - November 27-28, 1997, Paris
Journal: Journal de Mycologie Médicale

Swedish Society for Clinical Mycology
President: J. Faergemann
Vicepresident: T. Kaaman
Secretary: G. Pålsson
Treasurer: L. Edebo *(ECMM delegate)*
Membership 1996: 97
National meeting: Autumn 1997, Göteborg
Newsletter

Swiss Mycological Group
ECMM delegate: M. Monod

Turkish Microbiological Society Mycology Section
President: Ö. Ang
ECMM delegate: E. Tümbay
Membership 1996: 21

The Third Meeting of the ECMM 9-11th May 1996

The 1996 meeting of the Confederation was hosted by the Portuguese Society in the interesting city of Lisboa. The 260 delegates converged on the Alfa Hotel near the center of the city to hear the verbal communications and read the 100 plus posters scientific sessions started with the History of Medical Mycology in Brazil. There were round table sessions on systemic mycoses in immunocompromised host, public health mycology and dermatological mycology, these were thought provoking and excited some debate. Other invited speakers from Europe, USA and Brazil covered a wide range of topics including taxonomy, pathogenesis, clinical mycology, epidemiology and molecular mycology. New therapies for mycoses were presented and the susceptibility testing for antifungal drugs was discussed. There was also a session on veterinary aspects of mycology.

There was a programme of Portuguese entertainment most evenings and tours of the city were available. A boat trip on the river Tagus at sunset rounded off the social events.

The Lisboa meeting will long be remembered for its organisation and the excellent chance it afforded the participants to reacquaint themselves with old friends, make new friends and exchange ideas.

The fourth meeting of the European Confederation of Medical Mycology will take place in Glasgow, 11th-13th May 1998. I look forward to welcoming The ECMM to Scotland.

Gillian S. Shankland

A joint ISHAM-ECMM session

At the 13th Congress of the International Society for Human and Animal Mycology (ISHAM), which will be held in Parma, Italy, 8-13 June, 1997, a session organized jointly by ISHAM and ECMM will be dedicated to “Imported mycoses in Europe”.

The symposium, chaired by Prof. Bertrand Dupont and Dr. David Warnock, will include reports by:

• B. Dupont (France): Histoplasmosis in France 1970-1995
• T. Sirisanthana (Thailand): Diagnosis and management of Penicillium marneffei infection
• C. Kauffman (USA): New developments in the diagnosis of endemic mycoses
• D. Warnock (UK): Imported mycoses: risks for European laboratory workers.

Epidemiological Working Groups of ECMM

The first number of the Newsletter coincides with the setting up of the first ECMM Working Groups, which are concerned with epidemiological monitoring of fungal infections diagnosed in Europe.

There is much work to be done in this area as epidemiological knowledge is still too scanty, being limited to some countries with national societies interested in the topic. In fact, a map of the frequency and distribution of fungal infections in Europe is still lacking, and it is necessary to clarify their aetiology, pathogenesis, clinical aspects, diagnosis and therapeutic approach. The construction of such a map is one of the major aims of our Confederation.

The ECMM Executive Committee, in close contact with the Council, has approved the proposals for the constitution of the first five Working Groups. It has appointed a convenor for each study and has approved the regulations, which establish the organizational structure of the epidemiological working groups and ensure that collaborators will be able to work in harmony while at the same time each one's rights are respected. The regulations are published on the next page. The Working Groups approved to date are:

Survey of cryptococcosis in Europe
Convenor: Dr. Françoise Dromer
Survey of histoplasmosis in Europe
Convenor: Prof. E. Glyn V. Evans
Survey of nocardiosis and other aerobic actinomycetes infections in Europe
Convenor: Dr. Patrick Boiron
Survey of candidemia in Europe
Convenor: Prof. Renée Grillot
Survey of tinea capitis in Europe
Convenor: Prof. Roderick J. Hay

In each Working Group the Convenor will collaborate with a National Coordinator in each country. The latter will be responsible for stimulating the participation of various researchers in that country in order to collect a sufficient number of cases and collate, check and transmit the data to the Convenor. The National Coordinators are chosen by the Convenor, and candidates for this role in any of the above studies should promptly inform the Convenor of his/her availability.

A presentation of each study and the Convenor's address are published in the following pages. The name of the National Coordinator can be obtained from the Convenor or from the local ECMM delegate (for the list of delegates, see page 2).

The respective case record forms for the studies are also included. They have been designed based on previous experiences, and the aim was to make them as clear and simple as possible to facilitate participation. We suggest keeping the copy of the printed forms as master copies that can be photocopied each time that a case is to be reported.

The form, with all sections completed, should be sent to the local National Coordinator, together with the strain isolated in the studies only when diagnosis is based on culture. "Ownership"of the strains will be protected according to paragraphs "Isolates" and "Authorship" of the «Rules for Epidemiological ECMM Working Groups».

The planned duration of each study is 2 years. However, at the ECMM Congress to be held in Glasgow in 1998, a special session will be reserved for the presentation and discussion of the preliminary results of each study.

Maria Anna Viviani

Rules for Epidemiological Working Groups

A Working Group is composed of a Convenor (appointed by the Council), of several national coordinators (one in each country which wants to participate) and of local investigators. Convenor and coordinators have to be members of their national Society.

A study has to be approved by the Council on the basis of submission of a short project outline making clear the background and the goals of the study.

The collection of data requires a form that will be prepared by the Convenor with the help of some experts in the field (including a statistician). When the form is ready, an announcement will be made in the ECMM Newsletter. This announcement will include a summary of the study, the form, and an application form allowing people who are interested in participating to send their name, address, affiliation and country to the Convenor. Those who wish to be the coordinator of the study for their country will be able to apply at the same time.

This will allow the Convenor to select national coordinators (no more than 1/country) on the basis of their willingness to participate and their expertise in the field. Participants can also provide help in selecting the appropriate coordinator.

National coordinators will be responsible for collecting the forms, checking they are properly filled, helping local investigators if necessary and forwarding the forms to the Convenor. If a coordinator has to resign, the Convenor of the study will select another coordinator (and not the other way around).

Convenor and coordinators can only be involved in one epidemiological study for the ECMM.

When the Group is formed (Convenor+ coordinators), the Convenor has to inform the General Secretary of their names. He is also expected to submit a progress report to the General Secretary each year. The General Secretary is responsible for co-ordinating the work of the different Working Groups.

The Convenor of a study has to check with the local delegate or the administration of his country if there are any regulations on data collection, especially when using personal information on the patients.

Isolates

For all the epidemiological studies, it would be important to list centres (one or several) that will be able to collect the fungal isolates. This will allow a check on the identification and storage of isolates for future studies.

At the request of the depositor, the isolates will be maintained in a restricted collection, i.e. will not be sold or given out without authorization.

If a subsequent study is designed that requires the use of isolates stored from a previous study, all the mycologists who participated initially will be invited to join the new group.

Authorship

It must be clear that all participants will co-author the paper published by the Group. However, rules for authorship should be as follow

- The Convenor will be the first author.
- The coordinators will follow in a list ranked by the number of forms collected and, in case of equal contribution, in alphabetical order.
- The Study Group will sign last on behalf of the ECMM and the participants will be listed in alphabetical order of the country and then in alphabetical order of the last name for each country. Each coordinator will be responsible for the accuracy of the list.
- In case of a study involving isolates collected previously, the Study Group will include the members whose isolates are used even if they do not participate in the second study.
- Before submission to a Journal, the paper should be reviewed by all the coordinators and an agreement reached. Participants from each country will be informed by the coordinator. A copy of the final paper should be sent to the General Secretary.

Epidemiological Survey of Cryptococcosis in Europe

Convenor
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Aim of the study

Cryptococcosis, a life-threatening opportunistic fungal infection, is not among the diseases with mandatory notification around the world. This explains why there is very little information concerning the incidence among groups at risk such as AIDS patients, cancer patients or organ transplant recipients. The natural history of cryptococcosis is still not well known. Recent studies have suggested that there are differences among the serotypes of *Cryptococcus neoformans* regarding the type of host infected and the lesions caused by the fungus.

The main purpose of this ECMM study is to collect information on the patients infected by *C. neoformans* and on the infecting serotypes. A simple form will allow us to identify the risk factor(s), the extent of the dissemination at diagnosis and the initial treatment. Isolates will then be serotyped and the data analyzed.

Study design

Cases of cryptococcosis, for which the infecting isolate is available, will be recorded on a questionnaire (one-page long) and the corresponding isolate will be serotyped in one of the reference laboratories.

"Ownership" of the strains will be protected accordingly to paragraphs "Isolates" and "Authorship" of the «Rules for Epidemiological Working Groups».

Investigators interested in participating to this study as "national coordinator" are requested to fill the following form.

Name *first and family name* .....

Title: .....

Address: .....

.....

.....

Country: .....

Phone: .....

Fax: .....

E-mail: .....

EPIDEMIOLOGICAL SURVEY OF CRYPTOCOCCOSIS IN EUROPE

PATIENT DETAILS *report first 3 and 2 letters of the names*

Family name |__|__|__| First name |__|__| Year of birth |__|__|__|__| Sex: ☐ M ☐ F

Continent of birth: ..... Country of residence: .....

(for America specify South, Central or North)

RISK FACTORS *check all boxes needed*

- ☐ HIV infection CD4/mm³ .....
- ☐ Cryptococcosis = AIDS-defining disease
- ☐ Corticosteroid therapy (≥ 0.5 mg/kg/d) *reason* .....
- ☐ Autoimmune disease *specify* .....
- ☐ Organ transplantation *specify organ* .....
- ☐ Solid tumor/hematologic malignancy *specify* .....
- ☐ Bone marrow transplantation
- ☐ Fludarabine treatment
- ☐ Diabetes mellitus
- ☐ Cirrhosis
- ☐ Chronic renal failure
- ☐ Local injury
- ☐ Contact with pigeons or other birds
- Other *specify* .....
- ☐ Unknown risk factor

DIAGNOSIS OF CRYPTOCOCCOSIS *check all boxes needed*

Date *d/m/y* ..... ☐ New case ☐ Relapse

Suspected on the basis of:
- ☐ clinical symptoms *specify* .....
- ☐ X rays, CT scan, NMR *specify* .....
- ☐ screening for antigen

Antigen detected ☐ in serum *titer* ...../ ☐ in CSF *titer* ..... ☐ CSF pos.ve india ink

Cryptococcus neoformans cultured from:

☐ CSF ☐ not done	☐ blood ☐ not done	☐ BAL ☐ not done	☐ urine ☐ not done	☐ skin ☐ not done

other *specify* .....

INITIAL TREATMENT *check all boxes needed*

☐ amphotericin B ☐ 5-fluorocytosine ☐ fluconazole ☐ itraconazole

Other: ..... Daily dose .....

CORRESPONDING CLINICIAN/MYCOLOGIST *indicate name, address, phone and fax no., e-mail address*

.....

.....

SIGNATURE ..... DATE .....

Please, return the form together with the strain (specify from which sample it has been isolated), to your country's coordinator.

Epidemiological Survey of Histoplasmosis in Europe

Convenor
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Professor of Medical Mycology
PHLS Mycology Ref. Laboratory
Department of Microbiology
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United Kingdom
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Background
Histoplasmosis is a fungal infection caused by two dimorphic fungi, *Histoplasma capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii*. The disease caused by *H. capsulatum* var. *capsulatum* (from now on referred to simply as *H. capsulatum*) is a relatively common infection, endemic primarily in central and eastern parts of North America and parts of Central and South America, but occurring sporadically in many other tropical and subtropical countries world wide. Exposure to *H. capsulatum* by inhalation of conidia causes a mild pulmonary disease or is asymptomatic. In individuals with pre-existing lung disease or immunosuppression, this primary infection may lead to a secondary chronic or disseminated infection, which may be fatal. The prevalence of the disseminated disease has increased with the spread of AIDS and the increase in the number of immunosuppressed patients (e.g. transplant) in recent years. *H. capsulatum* var. *duboisii* infection, called African histoplasmosis or histoplasmosis duboisii is endemic only in Central and Southern Africa. It is a rarer disease that tends to cause subcutaneous and bone lesions and dissemination is rare.

Histoplasmosis in Europe
While not endemic in Europe, cases of histoplasmosis occur in individuals who have lived or travelled in endemic areas. There is often a history of exposure, for example, exploration of bat-infested caves. Reactivation of infections from several years previous may result from a failing immune system, as for example occurs in some AIDS patients. Chronic pulmonary histoplasmosis has also been seen in the last two decades in individuals who had not visited the endemic areas since the time of the second world war (e.g. Burma, 1944-45). In a recent study in France, 81 cases of histoplasmosis were recorded between 1970-94 and *H. capsulatum* was the causal agent in the majority of cases; in all cases, infections were believed to have been acquired outside Europe. Accurate information of the general prevalence of histoplasmosis in Europe is not available.

Objective of survey
The objective of this survey is to discover the prevalence of histoplasmosis in Europe, where and how the infection was acquired, the groups at risk, the organism responsible and the methods by which the infection was diagnosed. This will lead to a better understanding of this imported mycosis and will enable a co-ordinated effort to target at risk populations and to standardize methods for the diagnosis and treatment of the disease.
Investigators interested in participating to this study as "national coordinator" for their country are requested to fill the following form.

Name *first and family name* .....

Title: .....

Address: .....

.....

Country: .....

Phone: ..... Fax: ..... E-mail: .....

EPIDEMIOLOGICAL SURVEY OF HISTOPLASMOSIS IN EUROPE

PATIENT DETAILS *report first 3 and 2 letters of the names*

Family name |__|__|__| First name |__|__| Year of birth |__|__|__|__| Sex: ☐ M ☐ F

Country of birth: ..... Country of residence: .....

RISK FACTORS *check all boxes needed*

☐ HIV infection (CD4 /mm³.....) ☐ Transplantation *specify organ* .....

☐ Corticosteroid therapy *reason* .....

☐ Hematologic malignancy/solid tumor *specify* .....

☐ Occupational (within last year)

Exposure to birds/bird droppings *details* .....

Exposure to bats/bat droppings *details* .....

☐ Travel or residence outside Europe (within last 5 years)

USA/Canada *list states/provinces* ..... Dates .....

Other *list countries* ..... Dates .....

☐ Other *specify* ..... ☐ No predisposing factors

DIAGNOSIS OF HISTOPLASMOSIS ☐ New case ☐ Relapse

Date of diagnosis *d/m/y* ..... Date symptoms started *d/m/y* .....

Clinical symptoms *specify* .....

X rays, CT scan, NMR *specify* .....

Skin test ☐ positive ☐ negative ☐ not done

Antibodies detected by ☐ CF *titre* ..... / ☐ ID *band H,M* ..... ☐ not done

Antigen detected in ☐ serum *titre* ..... / ☐ urine *titre* ..... ☐ not done

Histoplasma capsulatum var. ☐ *capsulatum* / ☐ *duboisii* cultured from:

☐ BAL/sputum ☐ not done ☐ blood ☐ not done ☐ CSF ☐ not done ☐ urine ☐ not done ☐ skin lesion ☐ not done

other *specify* .....

Yeast cells seen in

☐ BAL/sputum ☐ not done ☐ blood ☐ not done ☐ CSF ☐ not done ☐ urine ☐ not done ☐ skin lesion ☐ not done

other *specify* .....

TREATMENT

Antifungal(s) given ..... daily dose ..... duration (to date) .....

CORRESPONDING CLINICIAN/MYCOLOGIST *indicate name, address, phone and fax no., e-mail address*

.....

.....

SIGNATURE ..... DATE .....

Please, return the form together with the strain, if available (specify from which sample it has been isolated), to your country's coordinator.

Epidemiological Survey of Nocardiosis and other Aerobic Actinomycetes Infections in Europe

Convenor
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Fax: +33 1 4568 8420
E-mail: pboironb@pasteur.fr

Aim of the study

There are few studies that address adequately either the epidemiology or the incidence of nocardial infections in human and animal populations. Since no agency or organization monitors diseases caused by *Nocardia* spp., the incidence of infections by these filamentous bacteria remains unknown. However, by analyzing the literature, some idea of the impact of nocardial infections on humans and animals is emerging. In addition, outbreaks of nocardiosis are described in several countries. Moreover, over the past 20 years, more reliable methods for classifying bacteria have refined the taxonomy of the actinomycetes. Consequently, many taxa formerly included in the genus *Nocardia* have been reclassified, while new species were discovered.

The other aerobic actinomycetes (*Rhodococcus, Gordona, Tsukamurella,* etc.) are also important potential causes of serious human and animal infections. However, because they are infrequently encountered in clinical practice, very little is known about these infections. The difficulties of diagnosis can lead to an underestimation of their real prevalence and incidence. An improved understanding of the epidemiology and pathogenesis of these infections will emerge when laboratories from different countries collaborate in an international epidemiological survey.

Because most members of the genus *Streptomyces* are saprophytes, their significance in clinical microbiology is generally overlooked. However, *Streptomyces* spp. are commonly isolated from human samples and several species are considered to be of potential medical importance. Several reports of *Streptomyces* infections have included septicemia and primary lung involvement, panniculitis, brain abscess, and cervical lymphadenitis. Evidence is growing that *Streptomyces* spp. should be added to the list of opportunistic organisms.

The main purpose of this ECMM study is to collect information on the patients infected by *Nocardia* spp. and other aerobic actinomycetes, and on the infecting isolates. A simple form will allow the identification of risk factors, the extent of the dissemination at the moment of diagnosis, the initial treatment, etc. Isolates will be (re)identified using classical and new molecular methods (PCR), and extensively characterized by means of various analyses including molecular typing (RAPD), plasmid analysis, *in vitro* antibiotic susceptibility testing, enzymatic characterization, potential pathogenic factors, etc.

Study design

Cases of nocardiosis and other aerobic actinomycetes infections, for which the infecting isolate is available, will be recorded on a one-page questionnaire and the corresponding isolate will be examined and characterized.

Investigators interested in participating to this study as "national coordinator" for their country are requested to fill the following form.

Name *first and family name* .....

Title: .....

Address: .....

Country: .....

Phone: ..... Fax: ..... E-mail: .....

EPIDEMIOLOGICAL SURVEY OF NOCARDIOSIS AND OTHER AEROBIC ACTINOMYCETES INFECTIONS IN EUROPE

(except Mycobacteria)

PATIENT DETAILS *report first 3 and 2 letters of the names*

Family name |__|__|__| First name |__|__| Year of birth |__|__|__|__| Sex: ☐ M ☐ F

Continent of birth: *for America specify South, Central or North* .....

Country of residence ..... Work .....

RISK FACTORS *check all boxes needed*

☐ Organ transplantation *specify organ* .....
☐ Corticosteroid therapy *reason* .....
☐ Chemotherapy *specify* .....
☐ Predisposing pulmonary disease *specify* .....
☐ HIV infection (CD4 /mm³ .....) ☐ IV drug abuse
☐ Other *specify* ..... ☐ No predisposing factor

DIAGNOSIS OF INFECTION *check all boxes needed*

Date *d/m/y* ..... ☐ New case ☐ Relapse

Strain identification .....

Strain cultured from:

☐ BAL ☐ sputum ☐ CSF ☐ pus *specify* .....
☐ biopsy *specify* ..... ☐ other *specify* .....

Positive direct microscopy ☐ *specify* ..... ☐ not done

Positive histology ☐ *specify* ..... ☐ not done

Main clinical, biological, radiological signs .....

.....

.....

Site of infection: ☐ lung ☐ brain ☐ skin ☐ other *specify* .....

ANTIBIOTIC TREATMENT *check all boxes needed*

Empiric treatment ☐ *specify* ..... daily dose .....

Specific therapy ☐ *specify* ..... daily dose .....

Cured ☐ yes ☐ no *if not, specify* .....

Life long suppressive therapy ☐ yes ☐ no *specify* .....

CORRESPONDING CLINICIAN/MYCOLOGIST *indicate name, address, phone and fax no., e-mail address*

.....

.....

SIGNATURE ..... DATE .....

Please, return the form together with the strain, if available (specify from which sample it has been isolated), to your country's coordinator.

Working Groups

Epidemiological Survey of Candidemia in Europe

Convenor
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Aim of the study

In order to better appreciate the current role of bloodstream infections due to *Candida* and *Torulopsis* spp. in hospitalized patients (cancer and non-cancer populations), ECMM has decided to develop a study, collecting information at the European level.

Indeed, there is a great need to increase the awareness of medical and biological practitioners who are still underestimating morbidity and mortality related to candidemia. High-quality clinical research in the difficult field of these fungal infections requires objective analysis of the epidemiological situation from a large multicenter study.

The main purpose of this survey is to integrate at the European level, in a simple form, information on cancer and non-cancer patients suffering from proven candidemia and concerning (i) the causative organisms of candidemia, the potential emergence of unusual species and the sources of the infection, (ii) the major underlying risk diseases or factors, (iii) the blood culture methods most often used in Europe to detect bloodstream pathogens, (iiii) the initial approach to management of a documented candidemia and the outcome of the disease.

Phenotypic (mycological profile and antifungal susceptibility testing) and genotypic studies on the isolates will be performed centrally.

Study design

Cases of documented candidemia will be recorded on a questionnaire (two-page long). The form and the corresponding isolates will be centralized in one national laboratory and the strains studied in reference centres.

"Ownership" of the strains will be protected accordingly to paragraphs "Isolates" and "Authorship" of the «Rules for Epidemiological Working Groups».

Investigators interested in participating to this study as "national coordinator" are requested to fill the following form.

Name *first and family name* .....

Title: .....

Address: .....

.....

.....

Country: .....

Phone: .....

Fax: .....

E-mail: .....

EPIDEMIOLOGICAL SURVEY OF CANDIDEMIA IN EUROPE

(*Candida & Torulopsis* species and their perfect form)

PATIENT DETAILS *report first 3 and 2 letters of the names*

Family name |__|__|__| First name |__|__| Year of birth |__|__|__|__| Sex: ☐ M ☐ F

Country & city of residence ..... Hospitalization date *d/m/y* .....

RISK FACTOR/PREDISPOSING DISEASE *check all boxes needed*

☐ General surgery *site of surgery* ..... date *d/m/y* .....

☐ Organ transplant *specify organ* ..... date *d/m/y* .....

☐ Burn % of burned body surface ..... date *d/m/y* .....

☐ HIV infection (CD4/mm^3 .....)

☐ Fetal immaturity birth weight ..... weeks of gestation .....

☐ Intensive care date of admission in ICU *d/m/y* ..... ☐ single/☐ multiple bedroom

☐ Antibiotics given within 2 weeks prior to blood yeast detection ☐ IV ☐ PO

type(s)/total dose .....

☐ Corticosteroids given at any time during the month prior to yeast detection in blood (exclude given with amphotericin B) *specify reason* .....

type(s)/total dose .....

☐ Hematological disease/solid tumor *specify* ..... diagnosed *d/m/y* .....

Disease stage at time of candidemia: ☐ onset ☐ complete/ ☐ partial remission ☐ resistant ☐ relapse ☐ other *specify* .....

Last therapy for underlying disease: started *d/m/y* .....

☐ 1st/ ☐ 2nd line chemotherapy ☐ auto/ ☐ allo BMT

☐ maintenance ☐ other *specify* .....

☐ Radiotherapy/ ☐ surgery within 1 month prior to candidemia (last done *d/m/y* .....)

☐ Other *specify* .....

DIAGNOSIS OF CANDIDEMIA *check all boxes needed*

Date of the first positive blood culture *d/m/y* ..... ☐ 1st episode ☐ relapse

Blood puncture from ☐ catheter ☐ vein

Blood culture system on which candidemia was diagnosed:

☐ Lysis centrifugation

☐ Bactec system ..... medium .....

☐ other system ..... medium .....

☐ combination *specify* .....

Species identified ..... Other fungus/bacteria isolated *specify* .....

Date of the last positive blood culture *d/m/y* .....

Total number of positive blood cultures/total number of blood cultures ...../.....

cont'd

OTHER CANDIDEMIA INFORMATION *check all boxes needed*

IV line

IV line in situ at time of the first positive blood culture ☐ no ☐ yes

☐ central venous catheter ☐ peripheral date of IV line placement *d/m/y* .....

IV line removed after the diagnosis of candidemia ☐ no ☐ yes

Catheter cultured ☐ no ☐ yes negative ☐ yes positive

☐ same yeast species ☐ other fungus/bacteria .....

Clinical & biological signs at time of candidemia

☐ Shock related to candidemia

☐ Organ involvement *specify organ* .....

Documented: ☐ clinically ☐ histologically ☐ by X-ray, CTscan, NMR

White blood cell count/mm^3 .....

Candidemia associated with:

☐ seroconversion increasing of ☐ antibody titre (>2 dilutions)/☐ bands

☐ antigenemia *specify test and titre* .....

Candida colonization, due to the same species, detected within 2 weeks prior to outcome of candidemia on

☐ oral mucosa ☐ not done ☐ resp. tract ☐ not done ☐ GI tract ☐ not done ☐ GU tract ☐ not done ☐ vagina ☐ not done ☐ skin ☐ not done

other *specify* .....

Antifungal(s) given within 2 weeks prior to candidemia: *reason* .....

type of antifungal ..... ☐ PO ☐ IV daily dose .....

Initial treatment of candidemia

☐ amphotericin B ☐ 5-fluorocytosine ☐ fluconazole ☐ itraconazole .....

other: ..... daily dose .....

Outcome (day 30): ☐ survival ☐ candidemia related complications ☐ death

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CORRESPONDING CLINICIAN/MYCOLOGIST *indicate name, address, phone and fax no, e-mail address*

.....

.....

.....

SIGNATURE ..... DATE .....

Please, return the form together with the strain (first isolate) to your country's coordinator.

Epidemiological Survey of Tinea Capitis in Europe

Recent informal discussions amongst European mycologists suggest that in some countries there has been a recent shift in the pattern of tinea capitis in favour of anthropophilic species. The objective of this survey is to identify the principle causes of tinea capitis in different European countries over a one year period - 1997-1998. It would be helpful to compare data from these years with any historical material and, if possible (ideal but not essential), collaborating centres should provide similar data from 1987-1988. The accuracy of the survey depends on the availability of laboratory confirmed diagnoses and participation in this survey would therefore be of potential interest to microbiologists/mycologists or dermatologists with access to diagnostic laboratory facilities.

As the numbers of patients are likely to be substantially higher than in the other ECMM surveys we have had to follow a different procedure for gathering data and at this stage we are hoping to identify all those who would be interested in participating in such a study.

We would like hear from all interested individuals or groups and, based on this initial call, would develop the data gathering exercise with as many as possible taking into consideration the need to obtain representative information from different regions in Europe.

Convenor
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1. Name of Centre ..... 2. Idnum (Leave blank) .....
3. Contact person and address: .....

.....

.....

4. Population served: ☐ Urban ☐ Rural ☐ Mixed
5. Usual source of material received in laboratory/clinic:

☐ Reference cultures only ☐ Routine diagnostic cultures only ☐ Mixed routine and reference

6. Approximate numbers of patients with confirmed diagnosis of tinea capitis or cultures from tinea capitis seen/received each year: .....

Thank you for your interest.
Please return to Professor R.J. Hay

Special report on...

3rd International Conference on Cryptococcus and Cryptococcosis

The *Cryptococcus* and Cryptococcosis Conference is a well recognized scientific appointment which every three years presents the state of the art of this area of medical mycology.
We have asked a chairman of each session to report briefly on recent advances presented and discussed during the meeting. We are pleased to be able to give a well delineated and exciting picture, a real monography, of all the aspects of this discipline. We are grateful to our colleagues for their invaluable, generous collaboration.

The third International Conference on *Cryptococcus* and Cryptococcosis was held at the Pasteur Institute in Paris on September 22-26, 1996. The meeting was organized by F. Dromer and B. Dupont from the Pasteur Institute, and K.J. Kwon-Chung from the National Institutes of Health in Bethesda. It took place in the new complex built recently after the donation of the Duchess of Windsor. The scientific community interested in *Cryptococcus* and cryptococcosis has increased in size over time (100 attendees in Jerusalem in 1989, 188 in Milano in 1992 and 205 in Paris). More than 50 oral communications and 62 posters presented by scientists coming from all over the world were presented on topics covering molecular biology and biochemistry, taxonomy, epidemiology and ecology, immune responses, pathogenesis, drugs and therapy, clinical manifestations and diagnosis, and cryptococcal polysaccharide. The meeting, summarized in the abstract book, and below by the persons chairing the corresponding sessions, offers a comprehensive view of the current knowledge on the disease and the fungus.
The result of the ballots collected during the meeting was announced at the end of the gala dinner at the Musée du Louvre. We are all enthusiastic to know that London will held the 4th Conference that will thus be organized by R.J. Hay and his colleagues in 1999.

Françoise Dromer

The opening lecture given by Prof. E. Drouhet and the closing remarks by Prof. F. Staib will be published in the forthcoming issue of the Journal de Mycologie Médicale.

Session I

chaired by
K.J. Kwon-Chung and J.R. Perfect

Molecular biology and biochemistry

Scientific program of the third International Conference on *Cryptococcus* and Cryptococcosis opened with the molecular biology and biochemistry session. There were a total of nine invited talks in the session; six on molecular biology and three on biochemistry. Since the transformation system was developed for *C. neoformans* in 1990, work on molecular biology of the yeast has proceeded on dissecting virulence factors, identification of drug targets and other important biological aspects of this pathogen. Drs. J.C. Edman and B.L. Wickes presented their works on the *MATα* locus and the *MATα* specific dimorphism. It was shown that the *MATα* locus of *C. neoformans* is significantly larger than any mating type loci known from other fungi and the locus is unique in that in addition to containing the expected genes for pheromone and homeodomain boxes, it is closely linked to at least two genes involved in signal transduction events. The pheromone gene induces a filamentous response when introduced into *MATα* strains. *MATα* strains alone can produce hyphae and basidiospores when cultured under certain conditions such as low concentration of carbon source, devoid of ammonia, dry substance (4% agar) and 25°C incubation temperature. Such phenomenon termed haploid fruiting or monokaryotic fruiting is common in basidiomycetes but only in *C. neoformans* it appears to be a mating type specific phenomenon. Since *MATα* strains are known to be more virulent than *MATa* strains, these *MATα* specific genes may be associated with regulation of other virulence genes such as *CNLAC1* or capsule genes.

Drs. S.D. Salas and P.R. Williamson both presented molecular aspects of the *CNLAC1* gene encoding a laccase which is known to be an important virulence factor of *C. neoformans* based on previous genetic studies. Molecular evidence that the melanin forming ability of *C. neoformans* is an important virulence factor was presented by Dr. Salas. He showed that virulence of a *CNLAC1* deleted isolate is significantly reduced compared to a wild type or a melanin negative mutant complemented with the wild type *CNLAC1* gene. The copper binding sites of the *CNLAC1* gene seem to be critical for laccase function since a missense mutation in one of the four putative copper binding sites of the gene abolished melanin forming ability. Dr. Williamson analyzed the 5' region of the *CNLAC1* gene and showed that there is a TATA box at position -539, upstream from the first translation site (ATG start codon) which could provide the DNA binding site for a transcription factor TFIID, CAAT box at position -503 and *Sp*1 site at position -1727. Electrophoretic mobility shift assays performed with nuclear extracts obtained from *C. neoformans* grown under repressed (glucose) as well as a derepressed conditions for laccase activity suggested that there are nuclear proteins that bind to these sites. The functional role of the *Sp*1 site in relation to *CNLAC1* remains to be elucidated. Plasmids containing inserts of sequentially deleted 5' regions were transformed into a *cnlac1* mutant strain in which the 5' segment of *CNLAC1* completely deleted. It was observed that transformants with plasmids containing the putative TATA box alone produced high levels of pigment while transformants with only open reading frame of *CNLAC1* showed no pigment. Glucose repression was reduced when the sequence upstream of -837 was removed. These data indicated the involvement of different segments of the 5' prime region in the regulation of *CNLAC1* expression.

Dr. J.R. Perfect reviewed progress in molecular biology of *C. neoformans* briefly and discussed a molecular model for potential antifungal target genes such as *ADE2* (phosphoribosyl aminoimidazole carboxylase), *NMT* (N-myristoyl transferase), genes occuring in the signal transduction pathway, and topoisomerases I and II. *ADE2* is a highly conserved house-keeping gene essential for growth of the organism but it may be possible to design specific inhibitors of the fungal *ADE2* protein with no effect on homologous host proteins. This is due to the fact that the *C. neoformans ADE2* protein has bifunctional catalytic enzyme activity and its intermediate structure is absent in the human purine pathway. Also discussed was an indirect approach for the identification of potential virulence genes and drug targets by comparing up-regulated and down-regulated genes in *C. neoformans* during infection of the central nervous system. At the present time, Dr. Perfect has identified four genes that are up-regulated within the CSF and the importance of these genes to virulence is being investigated.

Dr. J.N. Galgiani has identified a protein of approximately 20 kDa from culture filtrates of *C. neoformans* which stimulates a *Cryptococcus*-specific DTH response in mice. His laboratory is in the process of cloning the cDNA of this protein for the production of recombinant protein which can elicit a cell mediated immune response in mice immunized with cryptococcal antigens. There is a possibility that this protein may be a protease secreted by the fungus.

Of the three biochemistry pa-

pers, two were on antioxidative agents and one was on azole resistance. The first was presented by Dr. E.S. Jacobson who discussed the oxidation-reduction buffering by cryptococcal melanin. He demonstrated sequential reduction and oxidation of melanin and its modulation by Fe(II) using two types of modern electrochemical techniques: the potentiometric method in estimating the ratio of oxidized to reduced residues in melanin and the voltammetric method to deduce the oxidation state of melanin from the quantity of electrons which is able to accept a standard reduction scan. A melanin film generated from saponified 5,6-diacetoxyindole by cyclic voltammetry was used for measurements of oxidation and reduction. This study demonstrated that melanin is a redox buffer or electron exchanger.

Dr. S. Kelly studied possible biochemical causes of azole resistance in *C. neoformans* strains isolated from AIDS patients by examining the biochemical basis of variation in azole susceptibility and testing the potential for cross-resistance between azole and polyene antifungals. He found that the pattern of sterol accumulation in *C. neoformans* following azole treatment was different from that of *Saccharomyces cerevisiae*. Unlike the response in azole treated *S. cerevisiae* which accumulates lanosterol, obtusifoliol, 14α-methyl fecosterol and 14α-methyl-3,6-diol, *C. neoformans* accumulated eburicol and obtusifolione, indicating a block at the C4 demethylation step of 14α-methylated sterols. This suggests that sterol $\Delta^{5(6)}$ desaturation may be inhibited in *C. neoformans* while this reaction is not inhibited in *S. cerevisiae* or *Candida albicans*. Mutants of *C. neoformans* with cross-resistance to azole and polyene antifungals are readily isolated at a frequency of 10^{-8}, suggesting a single mutation responsible for cross-resistance. The mechanism of cross-resistance does not appear to have been associated with ergosterol biosynthesis. Rather, decreased uptake and increased efflux of the drug are the likely mechanism in these mutants. On the other hand, four mutants isolated from AIDS patients in whom fluconazole therapy failed showed cross-resistance to other azoles (itraconazole and ketoconazole) but were not resistant to polyenes. In these strains, the microsomal system was typical of fungi. Although they showed slightly elevated P450 content and slightly reduced azole levels in cells, the clear cause of resistance in these strains appeared to have been the nature of the sterol 14α-demethylase. The enzyme isolated from these strains was more resistant to azoles than that from a wild type when tested in cell free systems. These results indicated the existence of a wide range of biochemical causes of azole resistance in *C. neoformans*.

Dr. V. Chaturvedi presented evidence that the production and accumulation of mannitol contributes to the tolerance of fungal cells to heat, osmotic stresses and reactive oxygen intermediates (ROIs). He studied a mutant strain of *C. neoformans* isolated by mutagenesis which produces and stores significantly decreased amount of mannitol than its parental strain. In a previous work, this mutant was shown to be more susceptible to growth inhibition, killing by heat and high sodium chloride concentration, and have significantly decreased virulence in mice than the wild type strain. Since classical genetic analyses of this mutant did not succeed and a mannitol mutant isolated by gene disruption is not available, a glycerol-defective, osmosensitive *S. cerevisiae* mutant *Osg1-1* was used to show the effect of mannitol. The mutant *Osg1-1* was transformed with a multi-copy plasmid carrying *Escherichia coli mtlD* gene which encodes mannitol phosphate dehydrogenase. The *S. cerevisiae* transformant not only synthesized mannitol but restored osmotolerance in the strain. The transformant was less susceptible to killing by hydroxy radical and other ROIs. This study demonstrates *in vivo* that mannitol scavanges ROIs. There is a possibility that mannitol protects *C. neoformans* cells from killing by human neutrophils and thus contributing to virulence.

K. June Kwon-Chung

Session II

chaired by
D.H. Ellis and E. Guého

Taxonomy, epidemiology, and ecology

Dr. K.J. Kwon-Chung opened the session with an excellent review on the genus *Filobasidiella* which contains two unique species, *F. neoformans* (anamorph *C. neoformans*) and *F. depauperata* (no ontogenic yeast state known). Although these two species share nearly identical basidial morphology they have distinct life cycles, physiology and ecology. Of particular interest is the finding that *F. depauperata* is the first basidiomycetous fungus found to have its 5S rRNA genes dispersed throughout the genome, whereas in *F. neoformans* the 5S rRNA gene is located within the rDNA repeat unit. Thus the genus *Filobasidiella* is the first eumycotic genus found to have two distinct genomic arrangements of the 5S rRNA gene.

Dr. R. Petter then presented a paper examining the molecular divergence of the virulence factors of *F. neoformans* found in other heterobasidiomycetes. The phylogenetic tree construct on the basis of 17S rRNA sequences suggests proximal evolution of *Filobasidiella* and *Tremella* species and can best be classified in the order Tremellales, members of which produce encapsulated yeasts during their haploid state. A number of closely related members of the Tremellales were then screened for homologues of two virulence genes found in *C. neoformans*, viz the capsule gene *CAP59* and the melanin biosynthesis gene *CNLAC1*. The remainder of the session concentrated on the epidemiology and ecology of *C. neoformans* especially on the use of molecular characterisation of isolates which has proved to be a valuable epidemiological tool.

Dr. S. Kohno utilised both RFLP and RAPD methods to fingerprint clinical and environmental isolates of *C. neoformans* var. *neoformans* from Japan. He concluded that both clinical and isolates from pigeon excreta belonged to the same fingerprint type which provides additional evidence linking this environmental reservoir to clinical disease.

Dr. F. Dromer reported on the high incidence of *C. neoformans* var. *neoformans* serotype D infection in France (21% of isolates) and Italy (49% of isolates). A detailed analysis of 456 cases of cryptococcosis taking into account predisposing condition, age, sex and infection site suggested differences in terms of ecologic niche, virulence or tropism between serotypes A and D. The risk of being infected with a serotype D isolate was significantly higher in some areas of France and among patients with skin lesions and those receiving prolonged courses of corticosteroid therapy. Genetic similarities utilising DNA fingerprinting between clinical and environmental isolates were also demonstrated. Finally, differences in antifungal susceptibility were also found between serotype A and D isolates with the former being more resistant to therapy.

Dr. D. Ellis reviewed the worldwide distribution of *C. neoformans* var. *gattii* and reported on two new host eucalypt trees, *Eucalyptus rudis* and *E. gomphocephala*. The previous known host trees were *E. camaldulensis* and *E. tereticornis*.

Dr. M.T. Montagna et al. also reported the isolation of *C. neoformans* var. *gattii* from *E. camaldulensis* growing in Apulia, Italy. Further investigation of the range of host eucalypts for this fungus are warranted and detailed methods for the isolation of *C. neoformans* var. *gattii* were also presented.

Dr. D. Swinne highlighted the role of animals in the ecology and epidemiology of *C. neoformans* especially the association of serotypes A and D with pigeon and canary droppings. Other ecological niches such as hollows in trees and the potential for animal vectors were also discussed for both *C. neoformans* var. *neoformans* and *C. neoformans* var. *gattii*.

Finally, Dr. T.C. Sorrell presented data from 151 patients reported to the Australasian cryptococcal study group in the year to March, 1995.

David H. Ellis

Session III

chaired by
J. W. Murphy and L. Polonelli

Immune responses in cryptococcosis

The major focus of this session was on induction, expression, and regulation of cell-mediated immune (CMI) mediated resistance mechanisms against *C. neoformans*. The first two presentations provided information on direct interactions of lymphocytes with *C. neoformans*. NK cells from cryptococcosis patients with and without HIV infection were found to have reduced anticryptococcal activity. Treatment *in vitro* with IL-12 restored NK cell anticryptococcal activity in NK cells from HIV+ patients but did not upregulate anticryptococcal activity of NK cells from a limited number of non HIV infected individuals (R.G. Washburn).

Human and mouse T cells directly bind and kill *C. neoformans* and such T cell activity can be augmented in the mouse by immunization with heat-killed *C. neoformans* or by treatment of T cells with immobilized anti-CD3. Enhanced T cells with direct anticryptococcal activity did not correlate with protection (J.W. Murphy).

Several presentations covered cytokine and chemokine requirements for protection in cryptococcosis (G. Bancroft; M.F. Lipscomb, and G.B. Toews). Blocking of cytokines and chemokines such as IFNγ, TNF, MIP-1α, GM-CSF in the mouse model influences progression of cryptococcosis (G. Bancroft).

The type of TH cells induced and the cytokines influencing the induction and the relationship to severity of disease were defined in

mouse models (M.F. Lipscomb and G.B. Toews).

Cryptococcal polysaccharide in circulation has been shown previously to down regulate immune responses. Data were presented demonstrating reversal of this complex cascade of suppressor cells and factors could be achieved by treating mice with activated antigen presenting cells pulsed with GXM (R. Blackstock).

Enhanced anticryptococcal activity of macrophages treated with chloroquine was reported. The mechanisms of chloroquine enhanced anti-cryptococcal activity of macrophages was shown to be due to the chloroquine increasing the pH in the phagolysosomes of the macrophages (S.M. Levitz).

Finally antibodies to *C. neoformans* cytoplasmic antigens were described in sera from 20 patients with *C. neoformans* var. *neoformans* and 15 patients with var. *gattii* infections (A.J. Hamilton).

Juneann W. Murphy

Session IV

chaired by
J.E. Edwards and R.J. Hay

Pathogenesis and host responses

This section of the meeting was concerned with the interaction between cryptococcus and different host cells. In the first talk Dr. E. Blasi described the interaction between glial cells and yeasts. *Cryptococcus neoformans* is phagocytosed and destroyed by microglial cells in mice through nitric oxide mediated pathways. Certain cytokines such as IL-6 and IL-1β enhance destruction of *C. neoformans in vivo* in a mouse model. An avirulent *Candida albicans* strain can be given prior to challenge with virulent *C. albicans* to produce protection; however it does not protect against *C. neoformans* even though there are high levels of IL-1β and NO synthase mRNA being expressed. In contrast to the situation with *Candida*, after cryptococcal challenge there is delayed expression of IL-6 which may indicate immunomodulation by the encapsulated cryptococci.

Dr. J.E. Edwards described another potential effect of the capsule as more acapsular isogenic or mutant cryptococci are internalised by endothelial cells than the encapsulated forms. Internalisation, though, is needed for intracellular damage to take place; this effect is mediated through a heat labile mechanism. In contrast IFN-γ protects endothelial cells against cryptococcal mediated damage.

Interestingly Dr. A. Verheul and colleagues have shown that both intact *C. neoformans* and purified galactoxylomannan (GalXM) and mannoprotein (MP) components of the cell envelope can induce TNF-α production by macrophages. The role of the purified components depends on a heat stable mechanism. The MP, but not GalXM, in addition to both encapsulated and non-encapsulated *C. neoformans* enhance HIV replication in peripheral blood macrophages.

In studying the effects of *C. neoformans* on activation of CD4 and CD8 lymphocytes Dr. C.H. Mody showed that progression of CD8 cells beyond late G1 required the presence of CD4 cells. In addition phagocytosis is required for lymphocyte proliferation, an event which is inhibited by capsular material either *in situ* or presented in a purified form. However proliferation can be reversed by anticryptococcal capsular antibody demonstrating a potential mechanism for antibody in host defence against cryptococci.

In this section of the symposium new interactions between cryptococci and host cells which are involved in the pathogenesis of cryptococcosis have been described. The contributors have demonstrated different roles for the capsule and its components from inhibition, partial or total, of immune pathways and uptake of cryptococci to opsonisation of cells through anticapsular antibody.

Roderick J. Hay

chaired by
J.R. Graybill and D. Webb

Session V

Drugs and therapy for cryptococcosis

This session included a review of current treatment recommendations and also speculations on potential future treatment regimens using combinations of multiple drugs. In his opening presentation, Dr. W. Dismukes noted that at his university between 1990 and 1996 there were 91 cryptococcosis patients with HIV infection, but also a substantial number (58 patients) without HIV infection. The majority in both groups had meningitis, and in the non-HIV group the major predisposing factor appeared to be the use of corticosteroids. Since the advent of the amphotericin B-fluconazole sequential therapy for AIDS patients with cryptococcal meningitis, there has been less uniformity in approach to patients without AIDS. In the Alabama series there were 25 with meningitis, 24 with pulmonary disease, 3 with both, and 6 patients with other forms of disease. Treatment regimens included amphotericin B alone (13), combined with flucytosine (13), fluconazole alone (17) or fluconazole combined with flucytosine (3). Of those with pulmonary disease, 12 of 20 given amphotericin B ± flucytosine responded, versus 9 of 11 given azoles responded. There was only 1 relapse.

Standard therapy for cryptococcal meningitis in patients without AIDS has consisted of 4 to 6 weeks of amphotericin B (0.3 mg/kg/day) and flucytosine (>100 mg/kg/day). On the basis of the good results of the California Cooperative Treatment Group with an oral regimen of fluconazole and flucytosine in patients with AIDS, the Mycoses Study Group sought to compare such an oral regimen with initial treatment with amphotericin B and flucytosine followed by fluconazole 800 mg/day for 10 weeks (Pappas et al Abstract 73, Abstracts of the IDSA 34th Annual Meeting, New Orleans, 1996). Of 7 patients given the amphotericin B regimen, 6 were successfully treated, with follow up at one year, there was 1 failure and no deaths. However, of 5 patients on the oral regimen, there were 2 successes at end of treatment and one at one year. The other 4 patients died, including 2 deaths on treatment. Even though the numbers did not permit analysis, the study was terminated after the second death. Dr. Dismukes concluded that while a full course of amphotericin B and flucytosine was inconvenient and toxic, and that while part of the course may be shifted to fluconazole, there was little support to commencing with an all oral regimen.

Dr. R.A. Larsen reviewed a recently completed study of the California Cooperative Treatment Group, in which patients were escalated in cohorts with 400 mg increments from 800 mg through 2000 mg/day fluconazole. Within each cohort patients were randomized to no additional therapy or flucytosine. Responses were as reported in the table, defining success as conversion of CSF culture.

	Fluconazole		Fluconazole/flucytosine	
Fluconazole dose	N	% Resp	N	% Resp
800 mg	9	11	8	75
1200 mg	16	37	8	87
1600 mg	16	62	16	69
2000 mg	8	62	8	87

These data demonstrated both a dose response to fluconazole and an increased response when flucytosine was added.

Dr. B. Dupont reviewed the available data on prevention of cryptococcosis and maintenance therapy in AIDS and non-AIDS patients. A variety of published sources concurred that fluconazole, given either for thrush or cryptococcosis prophylaxis, was highly effective. Despite the wide use of fluconazole in France, however, there appeared to be little effect on the number of yearly cases reported to the French National Reference Center for Mycotic Diseases. This is surprising in view of recent data from the USA indicating a significant decline in cryptococcosis cases (1996 ICAAC). Many of us in the USA have experienced this (in my institution in San Antonio we have seen >50% decline in annual cases), and most attribute it to widespread use of fluconazole. Dr. Dupont concluded by noting that cryptococcosis in non-HIV patients is sufficiently rare to preclude primary prophylaxis. For secondary prophylaxis in non-AIDS patients there are few data, and Dr. Dupont recommended fluconazole at 200 mg per day for as long as any immune deficit persisted.

Finally, Dr. G. Just-Nübling pre-

sented a provocative open trial with a "triple regimen" of amphotericin B, flucytosine, and fluconazole conducted over 9 years. The median dose of amphotericin B was 930 mg/patient. Thirty eight patients received flucytosine at a median actual dose of 108 mg/kg/day, and 37 received fluconazole at 400 mg/day. Duration varied from 1 through 8 weeks. A complete response (clinical and negative CSF culture) was seen in 36/40 evaluable patients, and there were 3 partial responses and 1 failure. Two patients stopped because of toxicity. This trial impressed me for the high desired dose (150 mg/kg/day of flucytosine) and the general good tolerance of treatment. Also, the overall response of 90% is impressive, even higher than that claimed by the Mycoses Study Group in its recent trial of initial therapy with amphotericin B ± flucytosine.

Direct comparison is not possible because the conditions of the treatment (drug doses/duration, etc) were rather different. However, unpublished murine data by Larsen, Graybill, et al, suggest that triple drug therapy is superior to 2 drug treatment. Thus, Dr. Just-Nübling's approach may be reasonable.

John R. Graybill

Session VI

chaired by
B. Dupont and M.A. Viviani

Clinical manifestations and diagnosis

Three talks were focused on clinical manifestations and two on diagnosis.

Dr. J.E. Bennett first presented his experience on hydrocephalus and its management during cryptococcal meningitis in non-AIDS patients. Although rare (10/153 cases recorded at the NIH clinical center), hydrocephalus needs to be recognized in order to prevent deterioration of mental status. In the cases reported, hydrocephalus was discovered at various times following the diagnosis of cryptococcosis (simultaneously, to as long as 7 years). The major clinical sign present in all patients was dementia, usually associated with gait ataxia, but other signs such as papilledemia (1/10 patient) and cranial nerve palsies (2/10 patients) can be suggestive of hydrocephalus. In all cases, cerebral imaging was helpful and showed bilaterally dilated cerebral ventricles. Shunting provided neurologic recovery in 6, partial improvement in 3 and had no effect in one patient who had suffered several strokes before being shunted. Medical therapy was ineffective. Dr. Bennett thus emphasized the importance of cerebral imaging, when dementia is seen at any time during the course of cryptococcosis, and the importance of shunting, whatever the duration of the hydrocephalus has been, since there was no correlation between duration of symptoms and neurologic recovery.

Dr. R.J. Hay then spoke about extrameningeal cryptococcosis. He focused his talk on cutaneous cryptococcosis, describing and showing the various clinical and histological lesions encountered. Skin infection often reflects dissemination (in 50% of the cases for non-AIDS patients and almost all AIDS patients). Lesions can be solitary or multiple, following direct inoculation or fungemia, but a solitary lesion can be seen during disseminated cryptococcosis. Of note and still unexplained is the frequent association between *C. neoformans* serotype D and cutaneous lesions.

Dr. B.R. Speed reported the Australian data on cryptococcosis due to variety *neoformans* and variety *gattii*. Several parameters differ between the two varieties. The host preference is the most obvious difference since var. *neoformans* infects immunosuppressed patients whether infected or not by the HIV, whereas var. *gattii* is the main agent of cryptococcosis in immunocompetent hosts (74-80%).

Meningitis is more frequent in patients infected with var. *gattii*. Moreover, cerebral and pulmonary involvement associated with nodular lesions are more frequent. However, CT scan or MRI abnormalities can be seen during infections with both varieties. Infections with var. *gattii* are often difficult to cure by medical therapy alone and therefore often require surgery. The mortality rate is somewhat lower than with var. *neoformans* which can be related to the immune status of the host but sequelae are more frequent. Interestingly, patients infected with var. *gattii* had a greater antibody response than those infected with var. *neoformans*, further supporting the idea of differences in host response to the two varieties.

Detection of cryptococcal antigen was discussed by Drs. W.G. Powderly and E.G.V. Evans. Most of the commercialized tests have good sensitivity and specificity (≥95%), except when they do not recommend pretreatment of serum with pronase which decreases their performance. Their view was that titers <1:8 should be interpreted cautiously, especially in patients without risk factors. Positive antigen detection during routine screening of asymptomatic patients at risk for cryptococcosis, such as patients with AIDS, raises the question whether the patient should be considered as being infected or not. Since the natural history of this condition has never been studied, the answer cannot be unequivocal. The prognostic value of antigen titer evolution over time has been discussed. Several studies have suggested that a higher CSF antigen titer at baseline was predictive of a poorer prognosis in patients with AIDS, whereas serum antigen levels had no value. In a recent study by the Mycoses Study Group, a serum antigen titer <1:2048 and a CSF antigen titer <1:512 were predictive of culture negativity after 2 weeks of treatment. CSF monitoring of antigen titers seems overall the best means of checking the efficacy of acute therapy or the risk of relapse. An important issue in the interpretation of the results is the high variability in titers found for a given sample when commercial antigen kits and even laboratories are changed.

In addition to discussing antigen detection, Dr. Evans compared AIDS and non-AIDS patients for the positivity of India ink preparation (≤90% vs. ≤60%) and the positivity of CSF culture (>90% vs. 50-70%). Antibody detection has never been and will probably never be a means of diagnosing or even monitoring cryptococcosis, especially as antigen load prevents the detection of antibody during infection. Since cryptococcosis is the only opportunistic fungal infection for which the diagnosis is straightforward providing that the appropriate tests are carried out, very little has been made to develop DNA-based detection of *Cryptococcus* in clinical material.

Bertrand Dupont

Session VII

chaired by
J.E. Bennett and T.R. Kozel

Cryptococcal polysaccharide

The capsular polysaccharide of *Cryptococcus neoformans* is an essential virulence factor of the yeast. A session entitled "Cryptococcal Polysaccharide" explored the structure, genetic regulation and biological activities of the capsule. Dr. R. Cherniak provided a detailed description of the chemical structure of glucuronoxylomannan (GXM), the major polysaccharide constituent of the cryptococcal capsule. ^{13}C nuclear magnetic resonance spectroscopy for fingerprinting GXM structures provided evidence that the previously described simple structural relationship between polysaccharides of the four major serotypes was an oversimplification in many instances. Indeed, there is considerable variation in molecular structure of GXM within a given serotype. Drs. Y.C. Chang and K.J. Kwon-Chung described studies aimed at understanding genetic control of capsule formation. Three genes, designated *CAP59*, *CAP60* and *CAP64* have been isolated which are required for capsule formation and virulence. DNA sequence analysis has not provided an indication of the biochemical function for these genes.

Three reports described different biological activities of the cryptococcal capsule. Dr. T.R. Kozel discussed the ability of the capsule to served as a site for activation of the complement cascade and for binding of fragments of C3. Monoclonal antibodies specific for different epitopes of GXM were found to down-regulate, up-regulate, or have no effect on activation of the alternative pathway. These results suggest that GXM contains unique domains which regulate initiation and/or amplification of the complement system. Drs. D.L. Granger, D.M. Call and K.J. Kwon-Chung reported studies of the influence of the capsule on recognition of *C. neoformans* by interferon-γ-primed macrophages. Cells of the acapsular strain 602 induced nitric oxide synthase (NOS) expression by interferon-γ-stimulated macrophages. In contrast, there was little NOS activity by macrophages exposed to encapsulated wild type strains or to cells of strain 602 that were complemented to restore the capsule formation. These results suggest that the presence of a capsule masks the fungus from recognition by primed macrophages. Drs. Z.M. Dong and J.W. Murphy described the effects of glucuronoxylomannan, galactoxylomannan and mannoprotein on chemotaxis of leukocytes. The combined data showed that cryptococcal polysaccharides, especially GXM, act similarly to typical chemoattractants such as IL-8. GXM is chemotactic for human and mouse leukocytes; it induces L-selectin shedding from PMN and T lymphocyte surfaces; and it displays both pro-inflammatory and anti-inflammatory activities, depending on the distribution of GXM between extravascular and intravascular space, respectively.

Dr. A. Casadevall reported the development and *in vivo* activities of monoclonal antibodies specific for GXM, in particular, the ability of monoclonal antibodies to provide passive protection in a murine model of cryptococcosis. The protective capability of a monoclonal antibody depended on the fine specificity and isotype of the antibody. These results offer promise for the therapeutic potential of passive immunization and provide direction for vaccine research aimed at induction of protective antibodies.

Thomas R. Kozel

Mycology Courses in Europe (1997)

BELGIUM

Course on Medical and Veterinary Mycology
(every year)

Organizers: Proff. D. Swinne and Ch. De Vroey (lectures/aerobiology: Drs. N. Nolard, M. Detandt)
Address: Institute of Tropical Medicine,Nationalestr. 155, B-2000 Antwerpen, Fax +32 3 2161431
Duration-date: 5 months (one full day/week) - February to June
Hours theory/practice: Theory 30h / practice 70h
Admitted participants: 20
Certificate: Diploma

FRANCE

Cours de Mycologie Médicale ***(every year)***

Organizer: Dr. C. de Bievre
Address: Institut Pasteur, 28 Rue du Dr. Roux,75015 Paris, Fax +33 1 45688420
Duration-date: 8 weeks - 28 April-20 June 1997
Hours theory/practice: Theory 100h / practice 100h
Admitted participants: 20
Certificate: Diploma

Diplôme universitaire sur les mycoses systémiques*(every year)*

Organizers: Prof. B. Dupont, Dr. F. Dromer
Address: Institut Pasteur or Fac. Médecine Necker - Enfants Malades, 28 Rue du Dr. Roux, F-75724 Paris, Fax +33 1 45688218
Duration - date: 10 week (3h each week)-Mars to May
Hours theory/practice: Only theory
Admitted participants: 20 to 30
Certificate: Diploma

GERMANY

Course on Clinical Mycology*(every year)*

Organizer: Dr. K. Tintelnot, Robert-Koch-Institut, Bundesgesundheitsamt, Nordufer 20, D-13353 Berlin
Address: Working Group "Clinical Mycology" of DMykG
Duration - date: 2 days - 21-22 February 1997
Admitted participants: 25

Course on Experimental Mycology*(every year)*

Organizer: Dr. H.-J. Tietz, Zahnarzt, Facharzt für Mikrobiologie, Hautklinik der Charité, Schumannstr. 20/21, D-10117 Berlin
Address: Working Group "Mycological Laboratory Diagnostics" of DMykG
Duration: 2 days
Admitted participants: 30

POLAND

Course on Dermatological Mycology

Organizer: Prof. R. Maleszka and others
Address: Oddzial Dermatologiczny, 60-5 Poznan, ul. Dojazd 37
Duration - date: 5 days - September, 1997
Hours theory/practice: Theory 12h / practice 36h
Certificate: Diploma

Advances in Mycologic Dermatology

Organizer: Prof. Dr. hab. E. Baran and others
Address: Clinic of dermatology, 50-368 Wroclaw, Chalubinskiego 1
Date: 2 April, 1997
Admitted participants: 10
Certificate: Diploma

PORTUGAL

Course on Medical Mycology ***(every year)***

Organizers: Drs. M. Rocha, R. Velho, L. Rosada, J. Brandão, I. Costa
Address: ASPOMM, Centro de Dermatologia, R. José Estêvão 135, 1150 Lisboa, Fax +351 1 3522359
Duration - date: 3 weeks - 1-18 April, 1997
Hours theory/practice: Theory 35h / practice 40h
Admitted participants: 10
Certificate: Diploma

SPAIN

Course on Medical Mycology ***(every year)***

Organizer: Dr. Josep M. Torres-Rodriguez, Unitat de Microbiologia, Institut Municipal D'Investigació Mèdica, c/ Aiguader 80, E-08003 Barcelona, Fax +34 3 221 3237
Address: Departamento de Microbiologia, Fac. Medicina "UDIMAS", Universidad Autonoma de Barcelona
Duration: 3 weeks
Hours theory/practice: Theory 65% / practice 35%
Admitted participants: 15
Certificate: Diploma

SWEDEN

Course on Medical Mycology

Organizers: Drs. L. Edebo, J. Faergemann
Address: Sahlgrenska University Hospital, Dept. of Clinical Bacteriology, Guldhedsgatan 10, S-413 46 Göteborg
Fax +46 31 604975
Duration: 2 days
Admitted participants: 12
Certificate: Diploma

THE NETHERLAND

Course on Medical Mycology
(Dutch language edition)

Organizer: Centraalbureau voor Schimmelcultures, Baarn
Address: CBS, Oosterstr. 1, Baarn, Fax +31 3554 16142
Duration - date: 3 weeks - 1-19 April 1997
Admitted participants: 25
Certificate: Diploma
NB. A German language edition of this course for 60 participants will be held in Berlin, 3-15 March 1997

Course on Superficial Mycoses, for dermatologists

Organizer: Centraalbureau voor Schimmelcultures, Baarn
Address: CBS, Oosterstr. 1, Baarn, Fax +31 3554 16142
Duration: 2 days
Hours theory/practice: Theory 35% / practice 65%
Admitted participants: 25
Certificate: Diploma
NB. Several editions, either in Dutch or in English language, in The Netherlands and other countries

Course on General Mycology
(English language edition)

Organizer: Centraalbureau voor Schimmelcultures, Oosterstr. 1, Baarn, Fax +31 3554 16142
Address: CBS, and BioCentrum, Kruislaan 318, Amsterdam
Duration - date: 3 weeks - 24 February-13 March 1997
Admitted participants: 25
Certificate: Diploma

UNITED KINGDOM

BSMM Course on Diagnostic Medical Mycology

Organizers: Prof. E.G.V. Evans, Prof. R.J. Hay, and Drs. G. Midgley, L.J.R. Milne, M.D. Richardson, D.T. Roberts, D.W. Warnock and others
Address: c/o Prof. E.G.V. Evans, Dept. of Microbiology, University of Leeds, UK-Leeds LS2 9JT, Fax +44 113 2335640
Duration - date: 1 week - 7-11 April 1997
Hours theory/practice: Theory 15h / practice 18h
Admitted participants: 55

Master of Science in Medical Mycology
(every year)

Organizers: Prof. E.G.V. Evans, and Drs. R. Barton, D.J. Adams, H.R. Ashbee and others
Address: c/o Dr. H.R. Ashbee, Dept. of Microbiology, University of Leeds, UK-Leeds LS2 9JT, Fax +44 113 2335640
Duration: 1 year
Hours theory/practice: Theory approx. 150h /practice approx. 400h
Admitted participants: 20
Certificate: MSc, University of Leeds